June · 1961

American Perfumer

Proceedings

of the Annual Symposium

American Society of Perfumers

Start on Page 39

HEALTH SCIENCES
JUN 30 1961
LIBRARY

Abstracts from Society of Cosmetic Chemists . . . . Page 67

Synthesizing Chemicals and Biologicals by Microorganisms . . . . . page 27

Baby Shampoos . . . . . page 36

Product Design . . . . . page 71

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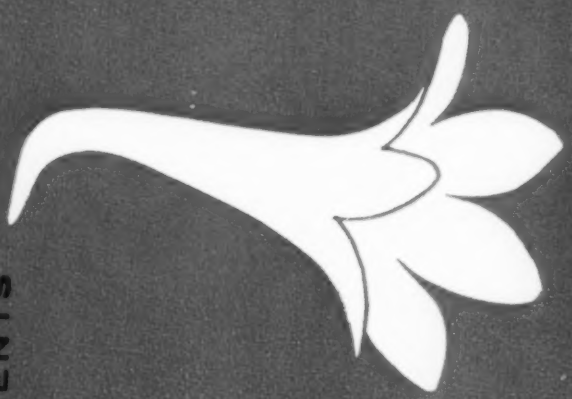

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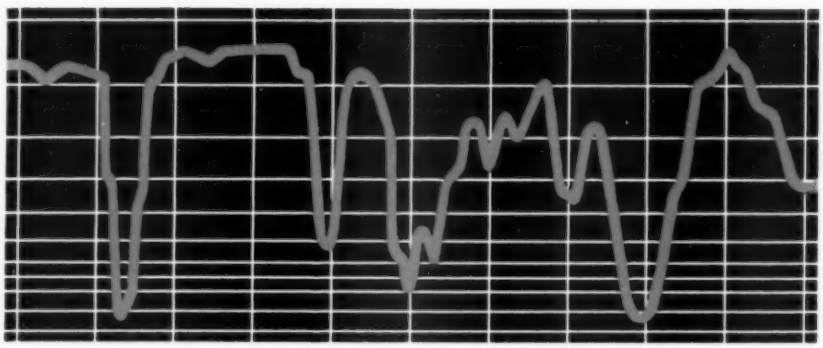

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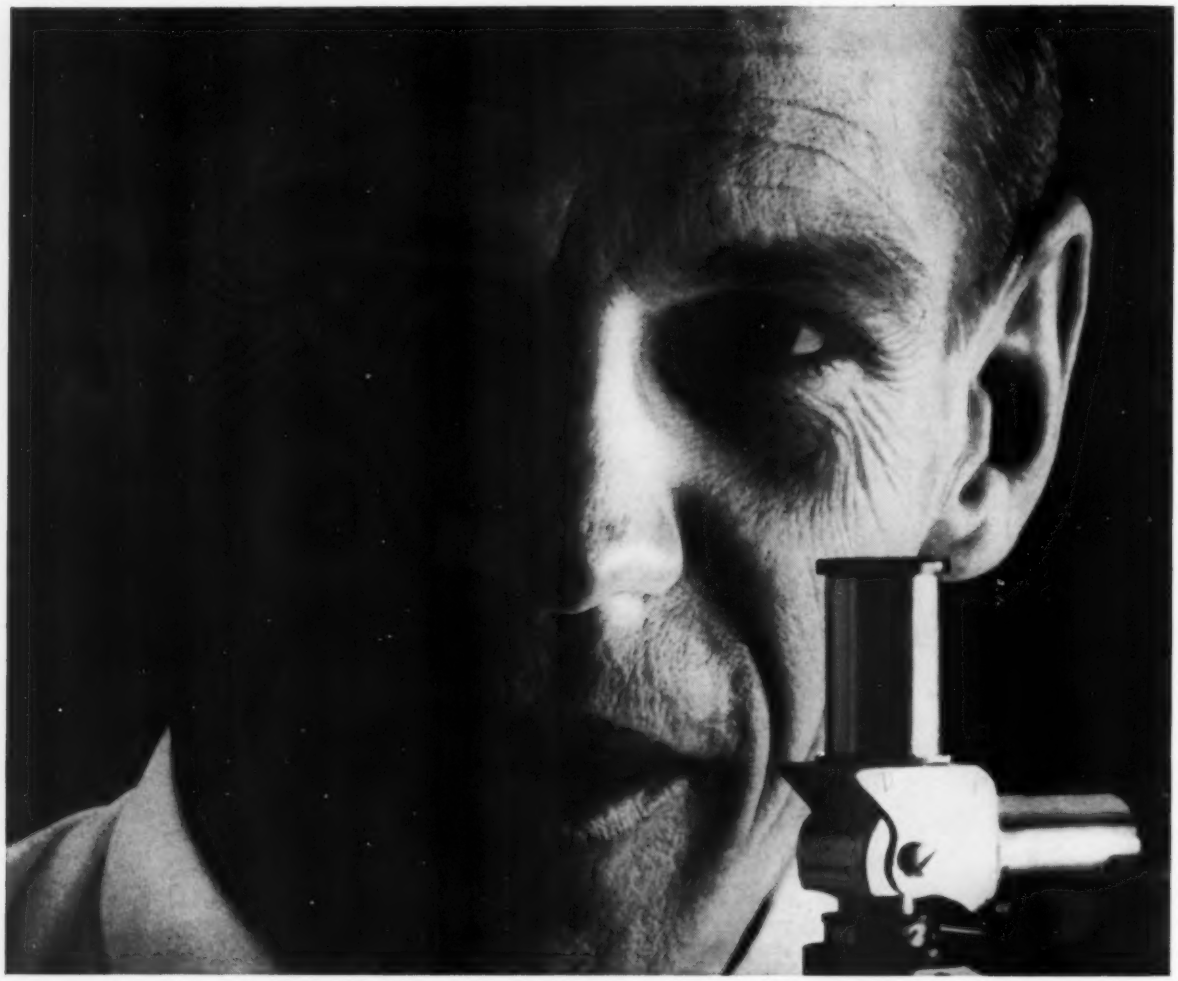

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American Perfumer

VOL. 76, NO. 6 June, 1961

Contents

Contenu
Contenido
Inhalt

Synthesizing Chemicals and Biologicals by Microorganisms ..... ***by Oldrich K. Sebek*** **27**

Alcohols are no longer the main fermentation products, since they can be synthesized more economically from petrochemicals. Fermentation is the preferred route for synthesizing larger organic molecules and certain organic acids.

La Synthétisation des produits chimiques et biologiques par des Microorganismes

Les alcools ne sont plus les produits principaux de fermentation, puisqu'ils peuvent être synthétisés plus économiquement par des produits pétro-chimiques. La fermentation est le procédé préféré pour synthétiser de grosses molécules organiques et certains acides organiques.

Sintetizando Productos Químicos y Biológicos por Microrganismos

Los alcoholes han dejado de ser los productos principales de la fermentación, ya que pueden ser sintetizados más economicamente de petro-químicos. La fermentación es la ruta preferida para sintetizar grandes moléculas orgánicas y algunos ácidos orgánicos.

Synthetische Zusammensetzung chemikalischer und biologischer Produkte durch Mikro-Organismen

Alkohole sind nicht mehr die wichtigsten Gärungsprodukte, da es rationeller ist, sie synthetisch aus Erdöl-Chemikalien herzustellen. Die Gärung ist der bevorzugte Weg bei der synthetischen Zusammensetzung grösserer organischer Moleküle und gewisser organischer Säuren.

Baby Shampoos ..... ***by H. S. Mannheimer*** **36**

A discussion of formulating this product so that it has non-stinging characteristics.

Schampooings pour Bébés

Une discussion sur comment préparer la formule de ce produit pour éviter que ce dernier ne brûle.

Champús para Bebés

Una discusión sobre la manera de formular este producto para que no produzca picazón.

Baby Schampun

Eine Besprechung der Formel-Zusammensetzung dieses Erzeugnisses, damit es keine brennende Wirkung ausübt.

Factors to Consider in Designing a New Product ..... ***by Walter G. Fredell***

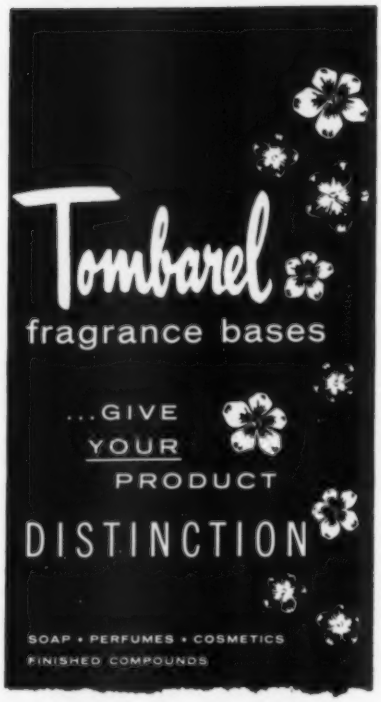
A check list of the many aspects of product design, with a typical example (anti-perspirant and deodorant) cited.

Quels sont les facteurs à considérer lorsqu'on prépare un Nouveau Produit

Une liste de références sur les nombreux aspects à considérer dans la fabrication d'un produit, avec un exemple typique (anti-transpiration et anti-odeur) mentionné.

Factores que se Deben Considerar al Oiseñar un Nuevo Producto

Una lista de los muchos aspectos sobre el diseño de productos, donde se cita un ejemplo (contra la transpiración y desodorante) típico.



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Faktoren, die bei der Schaffung eines neuen Produktes zu berücksichtigen sind
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Seventh Annual Symposium of The American Society of Perfumers . . . . . .

Preliminary Discussion of the Basics of Olfaction . . . . . ***by Dr. William Amols*** **41**

Author covers the physiological-psychological aspects of olfaction and discusses these influences on perfumes.

Discussion Préliminaire sur les Sous-Organes Olfactifs
L'Auteur couvre les aspects physiologiques-psychologiques d'Olfaction et en discute leur influence sur les parfums.

Discusión Preliminar de las Bases de Olfacción
El autor cubre los aspectos fisiológicos-sicológicos de la olfacción y discute sus influencias en los perfumes.

Einführende Besprechung der Grundlagen des Geruchs
Der Author behandelt die physiologischen und psychologischen Gesichtspunkte des Geruchs und bespricht deren Einfluss auf Parfums.

Identification of Odors . . . . . ***by Dr. Trygg Engen*** **43**

Present findings show that an average relatively-unpracticed observer can learn to identify correctly three levels of intensity. They could identify about 16 different odor qualities without error.

Identification des Odeurs
A présent il est démontré qu'un observateur avec une pratique relative peut identifier correctement trois niveaux d'intensité. Ce dernier peut identifier environ 16 odeurs différentes sans se tromper.

Identificación de los Olores
Los últimos descubrimientos nos demuestran que un observador escogido al azar y relativamente sin práctica, puede aprender a identificar correctamente tres diferentes niveles de intensidad. Pudiendo ellos identificar sin error unas 16 diferentes calidades de olor sin error.

Erkennen der Gerüche
Neuere Feststellungen zeigen, dass der durchschnittliche, relativ ungeschulte Beobachter es lernen kann, drei Stärkestufen richtig zu identifizieren. Es konnten ungefähr 16 verschiedene Geruchsqualitäten ohne Fehler festgestellt werden.

Physiology of Olfaction . . . . . ***by Dr. Don Tucker*** **48**

The possibility of going beyond the usual threshold studies of measuring olfactory response is presented.

Physiologie d'Olfaction
Il est possible d'aller au-delà des études pour mesurer la réponse olfactive.

Fisiolagía de la Olfacción
Se presenta la posibilidad de ir más allá del umbral conocido sobre los estudios de medición de reacciones olfatorias.

Physiologie des Geruchs
Die Möglichkeit wird gezeigt, beim Messen der Geruchs-Reaktion über die gewöhnlichen Grenzunterschungen hinauszugehen.

Odor and Molecular Constitution . . . ***by Dr. M. G. J. Beets*** **54**

The interaction between the stimulant and the receptor organ is discussed. This is characterized by the affinity of the molecule to the receptor surface and by its efficacy.

Odeur et Constitution Moléculaire
L'action réciproque entre le stimulant et l'organe réceptif y est discutée. Ceci est caractérisé par l'affinité du molécule sur la surface réceptive et par son efficacité.

El Olar y la Constitución Molecular
Se discute la interacción entre el estimulante y el organismo receptor. Esto se caracteriza por la afinidad entre la molécula hacia la superficie del receptor y por su eficacia.

Geruch und molekulare Konstitution
Die gegenseitige Wirkung zwischen dem Reizmittel und dem Empfangsorgan wird besprochen. Dies wird durch die Affinität des Moleküls zur Empfangs-Oberfläche gekennzeichnet sowie durch seine Wirksamkeit.

PRODUCT INFORMATION . . . **71**

FINANCIAL NEWS OF COSMETIC INDUSTRY **76**

DEPARTMENTS

Reactions 14
Desiderata 23
Technical Abstracts 67
Personalities 78
Classified Advertising 81
Industry Events 80
Professional Services 81
Index to Advertisers 82

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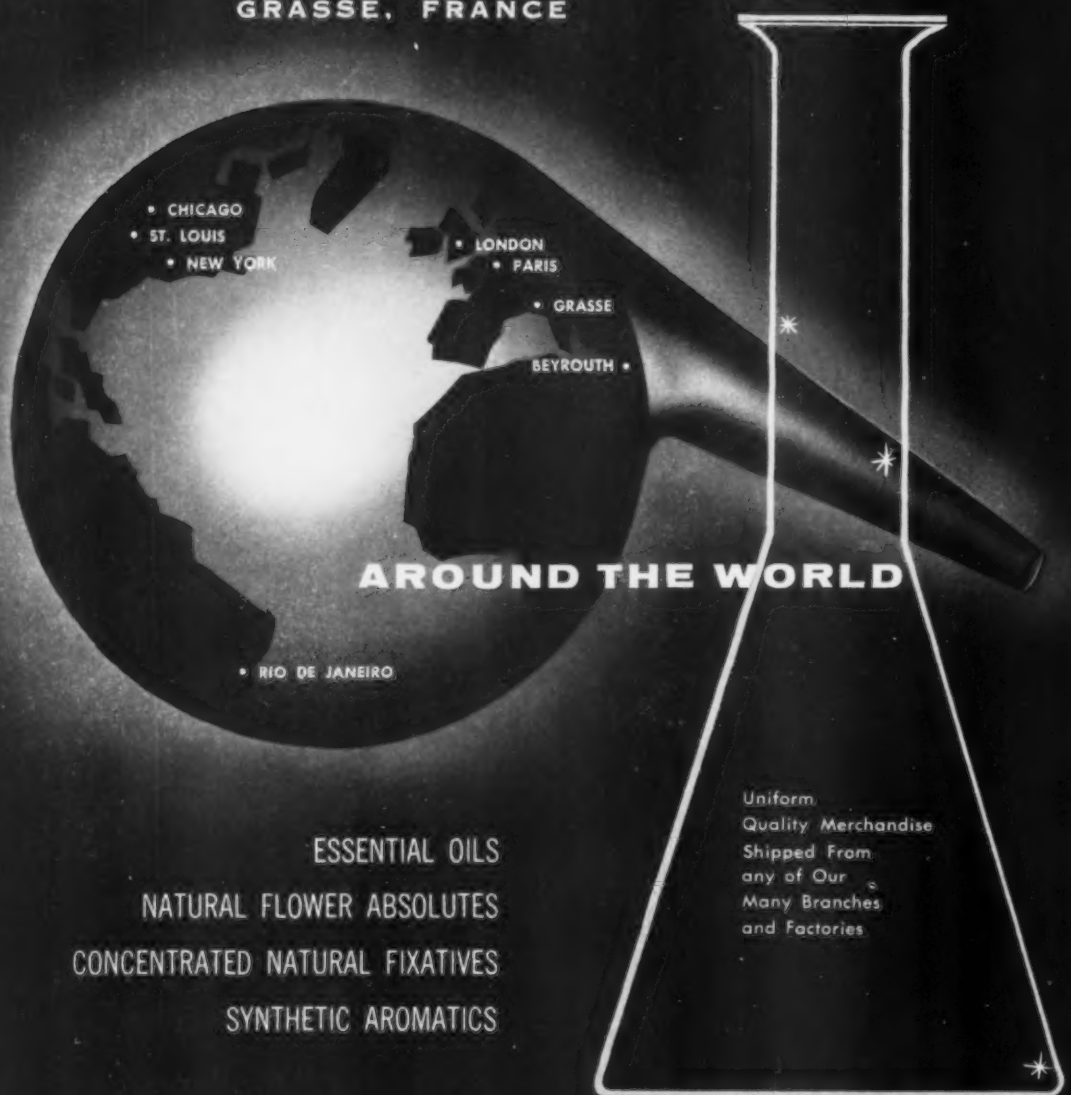

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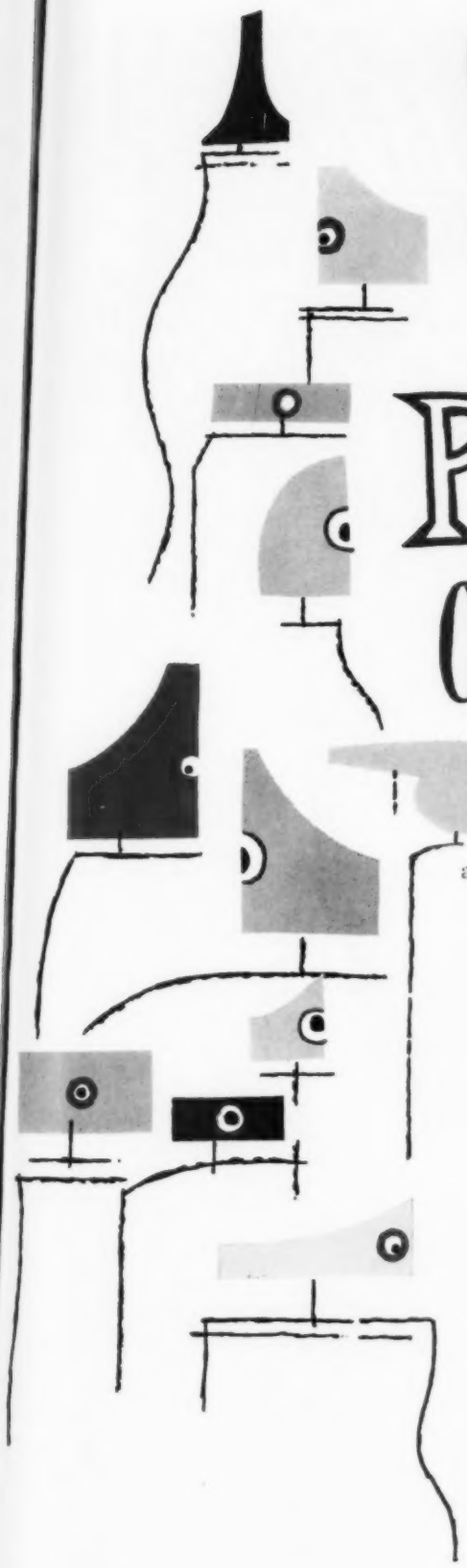

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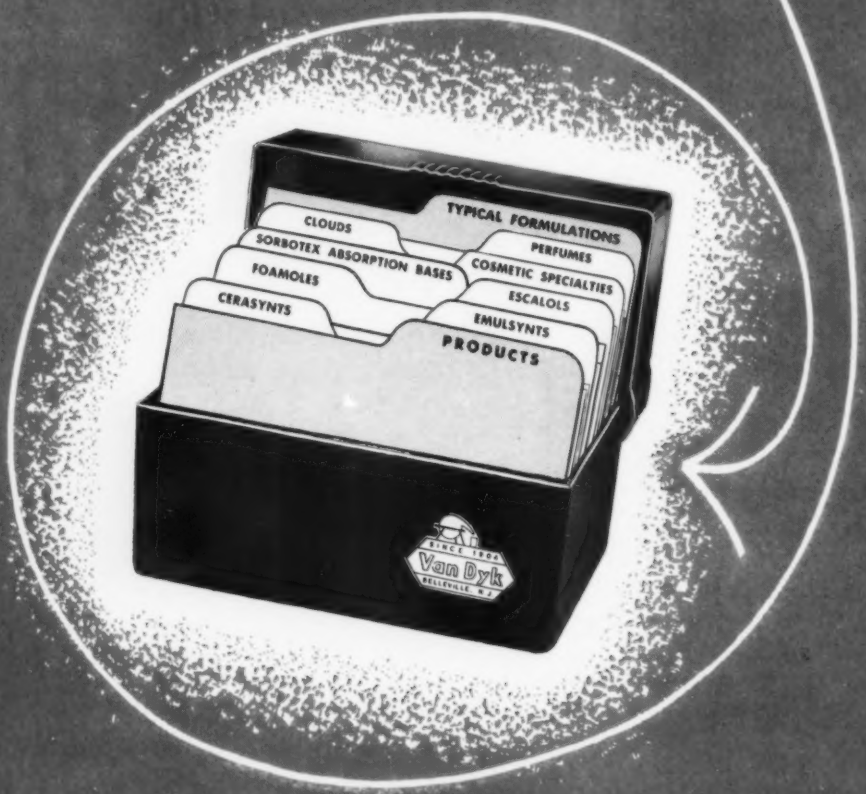

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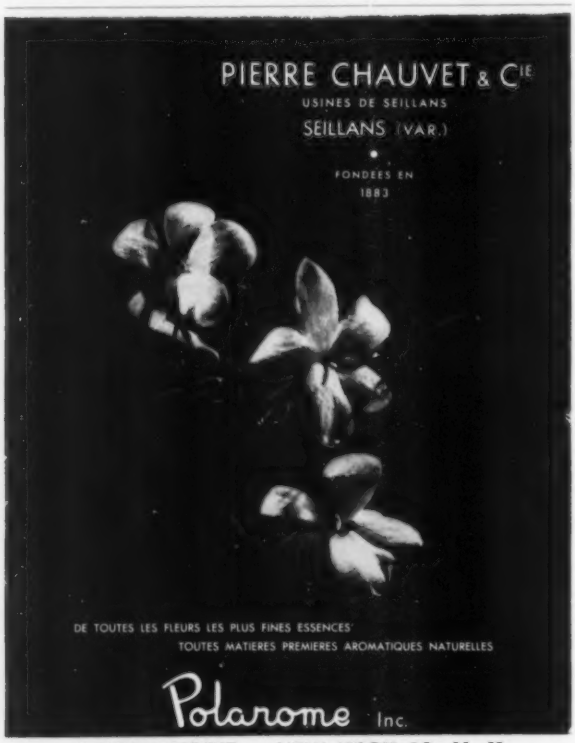

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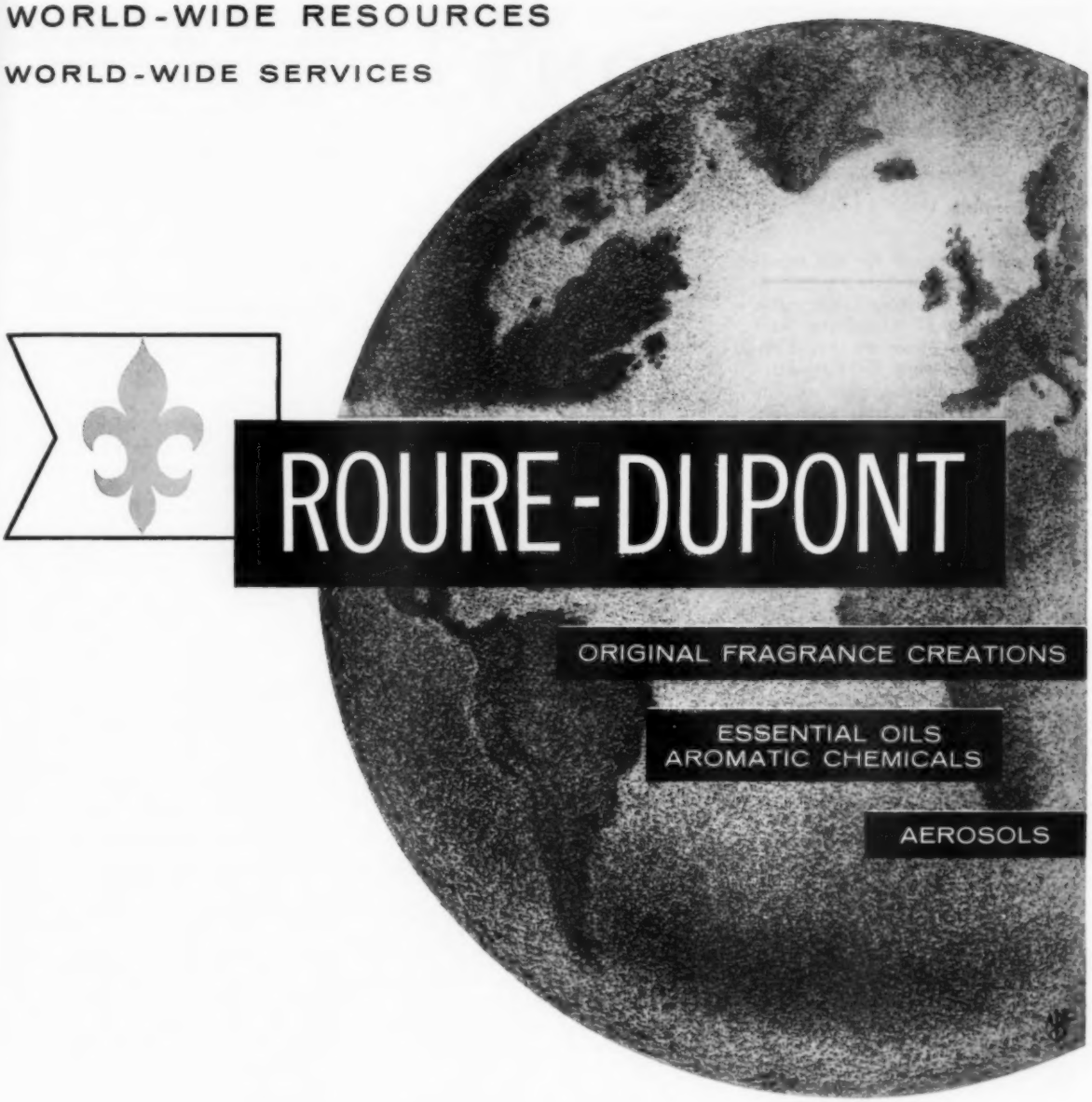

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REACTIONS

Wants Formula and book

Please send source for the report of the new ointment base reported in "Desiderata", AMERICAN PERFUMER, April, 1961, pg 17. Or, if you have a copy you can spare we would appreciate it. We want the formula.

At the same reference page we note you announce your forthcoming revision of your "The Chemistry and Manufacture of Cosmetics". Would you please give us the publisher and his address so we may write requesting notification of publication?

H.J.H.–Morgantown, W.Va.

The source of the report of the new ointment base as mentioned in "Desiderata", April 1961 issue of American Perfumer is: Martin-Valer Consultants, 23 E. 26th St., New York 10.

The revision of my book, "The Chemistry and Manufacture of Cosmetics" will be available from the Continental Press, 14812 Alma, Detroit 5, Mich.–M.G.deN.

Sorbic acid

In your article Sorbic Acid in the 1st Documentary Edition you state in a footnote that a report has appeared in the literature that sorbic acid may have a sensitizing potential.

As you may recall, sorbic acid tested in 1% hydrophilic petrolatum was included in my paper on patch test study published in the *Journal of Cosmetic Chemists* (June, 1961, 11, 249),

The repeat insult method of patch test performed on 50 subjects was negative as to allergenic action. If it is allergenic I believe it would have a low index if this test did not elicit such action. 1% in the above mentioned vehicle by closed patch test showed no evidence of primary irritant action. It would appear, therefore, .1 and .2% as used in cosmetics would have no primary irritant action.

I thought it would be of interest to you to call your attention to the result of this study.

Joseph V. Klauder, M.D.
Philadelphia 3, Pa.

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P.R. DeB., Washington, D.C.

We are glad to be of service–Editor

Correct equation

In my paper, "Application of Acid-Base Theory to Product Formulation" published in the April 1961 issue of AMERICAN PERFUMER, there was one error which should perhaps be noted. On page 31, the right hand side of the logarithmic form of equation (1) should have read:

$S = S_0 (1 = \text{antilog } [pH - pK_a])$

The internal parantheses were left out, inadvertently, and I failed to catch the error.

Robert J. Gerraughty, Ph.D.,
Assistant Professor of Pharmacy,
University of Rhode Island

Correction Please

The last footnote, page 21, January 1961 issue AMERICAN PERFUMER should read "Product of Keimdiat GmbH, Augsburg, Germany."

I would like to point out one small error that appeared in my biography with my article on Specialty Soaps in the March issue of AMERICAN PERFUMER. My company's address appears at Palmo, N. Y., whereas this is our cable address, rather than our business address. Our executive offices are at 15 East 26th St., New York 10, N. Y. and our plant and laboratories are on Division St., Boonton, N. J.

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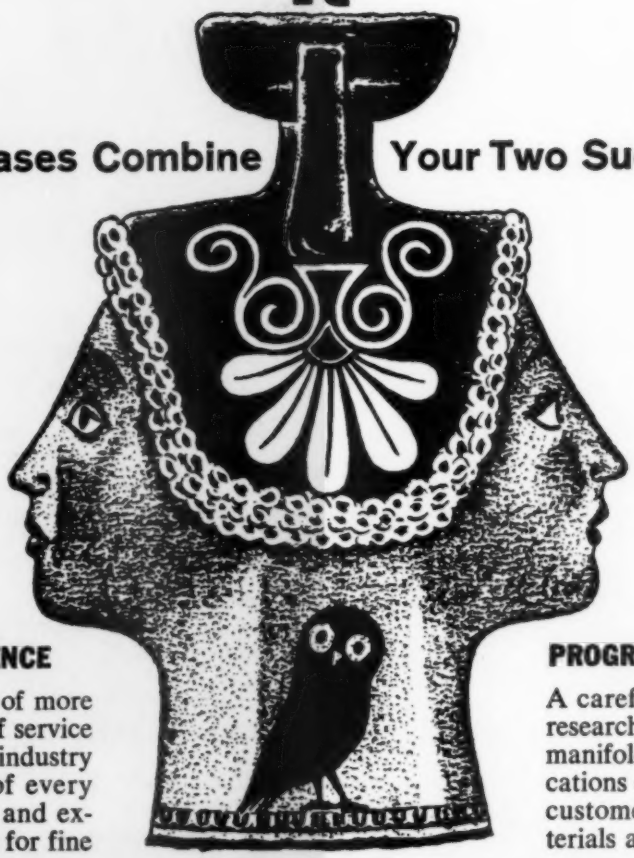

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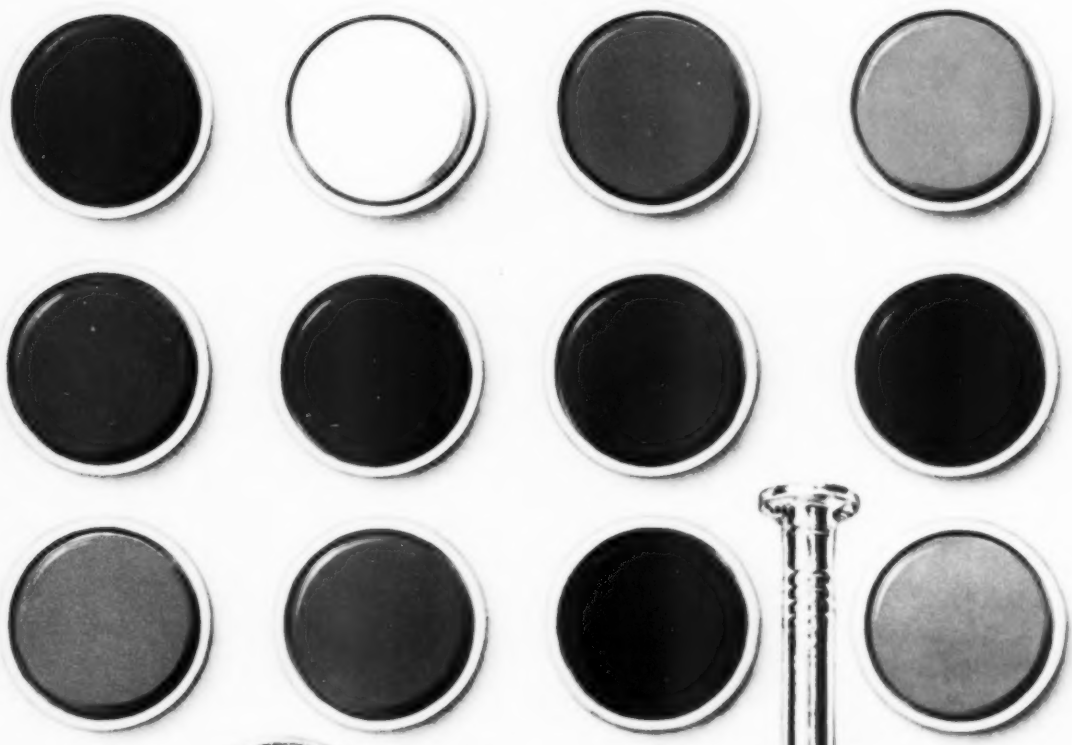

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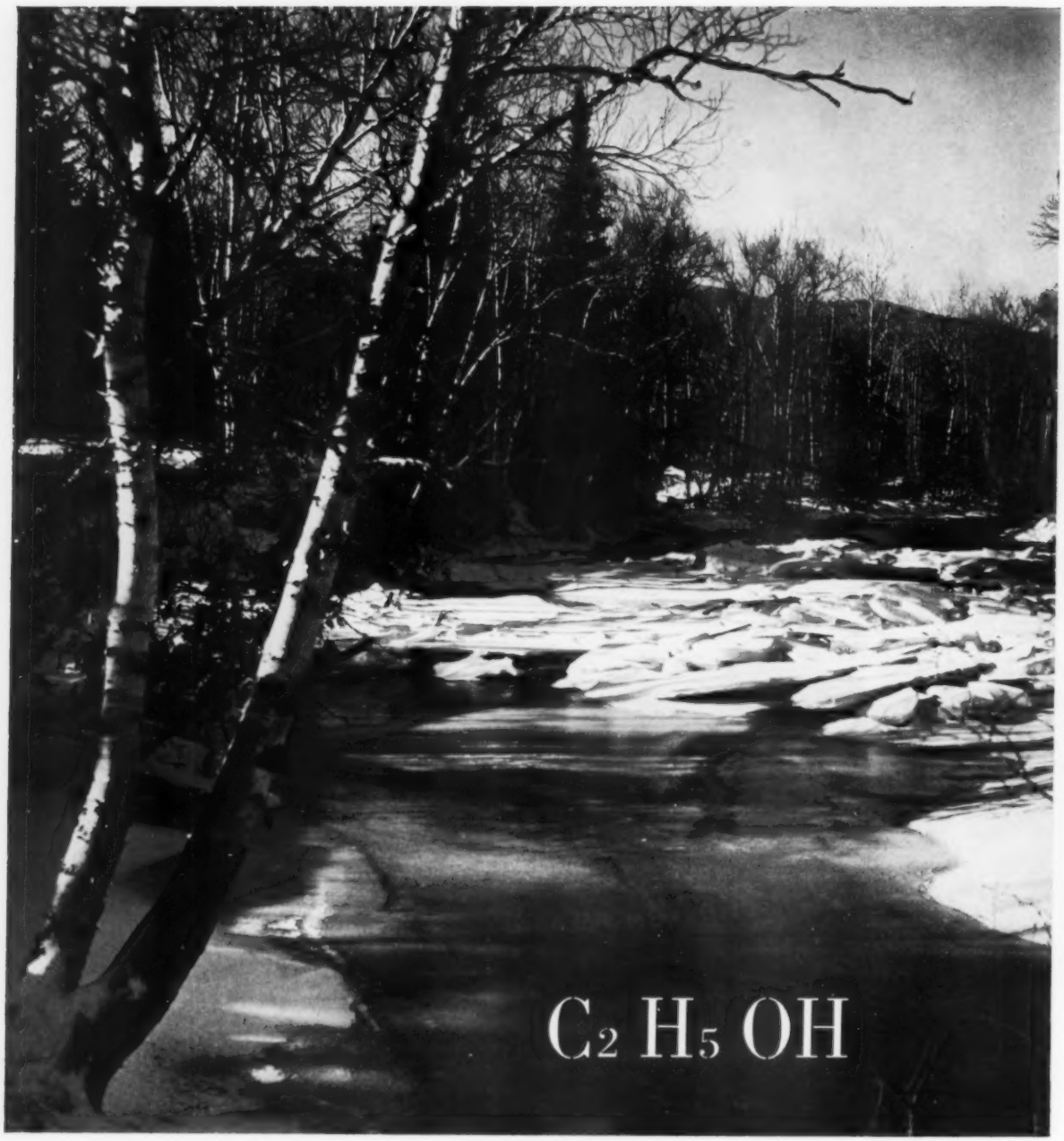

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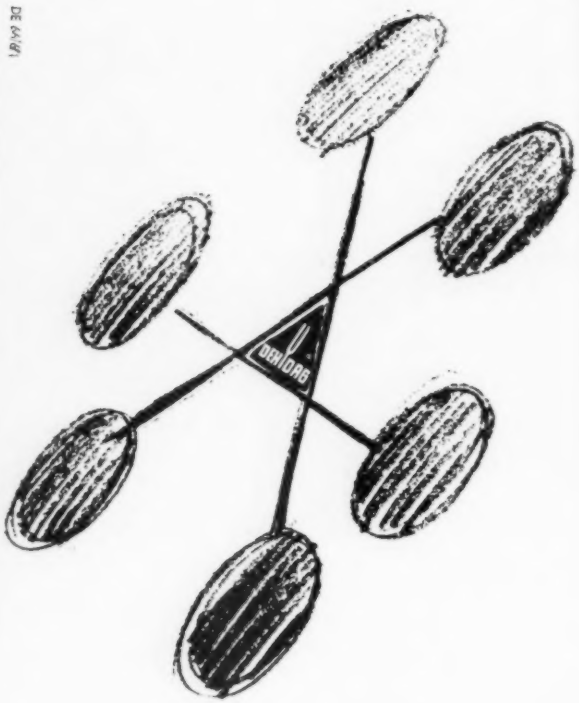

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Maison G. deNavarre, M.S., F.A.I.C.

Alkaline Phosphatase

It is commonly believed that there is little if any alkaline phosphatase in human skin.

But now it appears that hormones may induce the formation of alkaline phosphatase in human cells. Cox and MacLeod (Nature, *190*, 85, 1961) find that prednisolone can induce alkaline phosphatase activity in epidermal tissue. The acid phosphatase is not significantly altered. It is possible therefore, that other steroids may have a similar effect. If this is desirable, then the use of placenta extracts containing alkaline phosphatases may also be desirable?

Notes

It isn't often one has the opportunity to congratulate a fellow editor for receiving a special award. But it is a distinct pleasure to call to your attention that F. V. (Freddy) Wells, Editor of *Soap, Perfumery and Cosmetics*, has received the Guiliana Brambilla prize (see AMERICAN PERFUMER, March '61, p 83) for his contributions over the years as editor and author . . . . The banana is coming into its own again. Authors of a letter to the editor of the *J. Pharm. Pharmacol.* (*12*, p. 318) confirm the high 5-hydroxytryptamine content of the banana but find it reduces gastric acidity and secretion, preventing chronic ulceration of animal stomachs. So if you have an acid stomach or ulcers, it's the banana for you.

. . . . In the same tone, there are now indications that it is possible that cancer in humans may be due to overcooked foods, like scorched steaks rare, or medium etc.; smoked food may similarly be at fault. Stuff like bacon and ham and artificially "smoke treated" foods might be at fault in the case of stomach cancers in particular. . . . . You may have seen an editorial in the Jan.-Feb. 1961 *Clinical Pharmacology and Therapeutics*, discussing the number of drugs being introduced and the total now in existence. The figure ascribed to Barr was 140,000. Paul de Haen who knows this subject well, says this figure was taken from the Red Book which includes package sizes, dosage forms, toiletries and proprietaries. The actual number of drug products is probably no greater than 12,000.

Retirement

Those on the ragged edge of retirement or already there by choice or otherwise, will find an interesting bit of reading in the J.A.M.A. for May 6, 1961, dealing with thoughts on the retirement fad.

It was news to learn that it all started with Bismarck who felt men were finished at 65. The two doctors writing these observations poke considerable thought provoking fun at hobbies. Indeed, a good point is made of the fact that a man's work may be his hobby (mine is!). Happy is the man who can look back on a day's work without alarm; pity the man who after 8 hours of "dreary" work gets freedom at 5:00 p.m. to last only until 8:00 a.m. the next day.

The idea of old people looking for new hobbies is for the birds. Collecting stamps at this late date is no fun. Better to channel your energy into fields dealing with one's life experience. Preparation for old age "should be to teach against the fear of death . . . . life must be dull and drab, hobbies or no hobbies, for those who let each day arrive simply to bring them closer and closer to death".

Lipstick and cancer

In the J.A.M.A. (*172*, No. 7, p. 645, 1961) Jerome answers a query about possible carcinogens in lipstick as follows: "The Food and Drug Administration has indicated that many of the dyes presently used in lipstick formulations may contain traces of a cancer-inciting agent. This opinion is based on animal-feeding tests, and admittedly, the amount of dye that might be ingested into the human system from lipsticks is much less than the amounts used in the animal-feeding tests. We have no information on the effects of local applications".

We would all like to know Jerome's authority for these statements. The 17 lipstick colors questioned by F.D.A. were not carcinogenic. What then is the source of the statement "that *many* of the dyes presently used in lipstick for-

mulations may contain traces of a cancer-inciting agent".

FD & C Red #1 was not delisted because it was carcinogenic. The same would apply to lakes made from it. FD & C Yellows 3 and 4 were delisted because F.D.A. was not certain they could be produced with assurance that they do not contain B-naphthylamine as an impurity (HEW-033). To my knowledge these colors were never used in lipsticks.

The T.G.A. knows of no use of these colors in lipsticks, although Hueper did make the statement that they were so used about a year ago. His remark was based on observation of a lipstick mass having the appearance of cheese tinted with these yellow colorants. But Hueper had no proof that the lipstick was so tinted.

Such statements are damaging to the industry and of course give misinformation.

BOOK REVIEWS

Fachkunde der Parfumerie und Kosmetik, by Koll/Kowalezyk, 358 pages, illustrated and indexed. Fachbuehverlag Leipzig (Russian zone) 1959. 18 *DM.*

The text is divided into sixteen major groups with numerous subsections in each. Perfumery is dealt with first, requiring about 85 pages to complete the presentation at the end of which are a considerable number of formulas for such famous perfumes as Chanel 5, Arpege, Shalimar and numerous others. Unfortunately, all the formulas appear to come from one perfume compound supplier.

The general group of cosmetics is considered with numerous formulas. Illustrations are many and good.

The use of thioglycolates though described under hair waving, is not mentioned in the depilatory section. Alginates are not discussed with the dentifrices but many worn out "therapeutic" materials are still included.

These are but a few of the many examples that could be cited, showing that the book is incomplete and certainly not up to date insofar as formulas and methods are practiced this side of the Iron Curtain. The book's scope prevents completeness. Patents are hardly mentioned. Literature references scarce. An incomplete dictionary of cosmetic trade named materials is typical of the text.

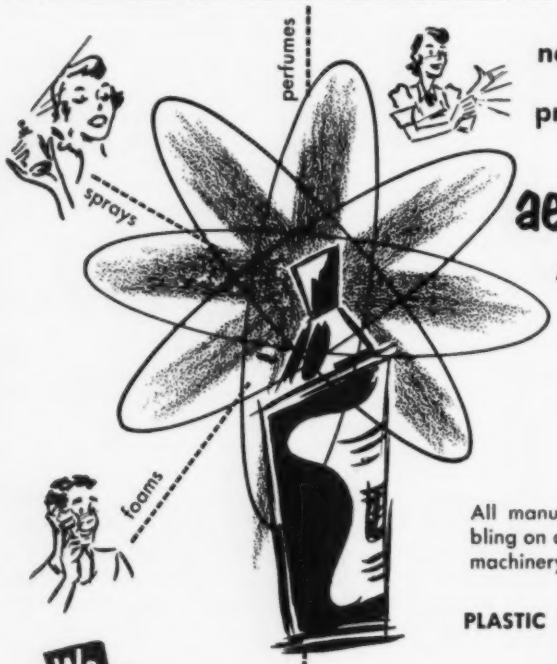
The book gives us an idea of the thinking behind the Iron Curtain and little more.—(M. G. deN.)

Industrial Chemicals, by W. L. Faith, D. B. Keyes and R. L. Clark, 844 pages, indexed and illustrated. John Wiley and Sons, Inc., New York 16, N. Y., Price $16.00.

This second edition follows the pattern of the earlier work. Thirty-five industrial chemicals are added to the previous 106, dropping only one. The data covers the years 1935-1956. No publication references are used. Materials reviewed start with acetaldehyde, ending with zinc oxide.

The format used gives much information on each ingredient.

Using stearic acid as an example, this reviewer finds the work quite complete.—(M. G. deN.)



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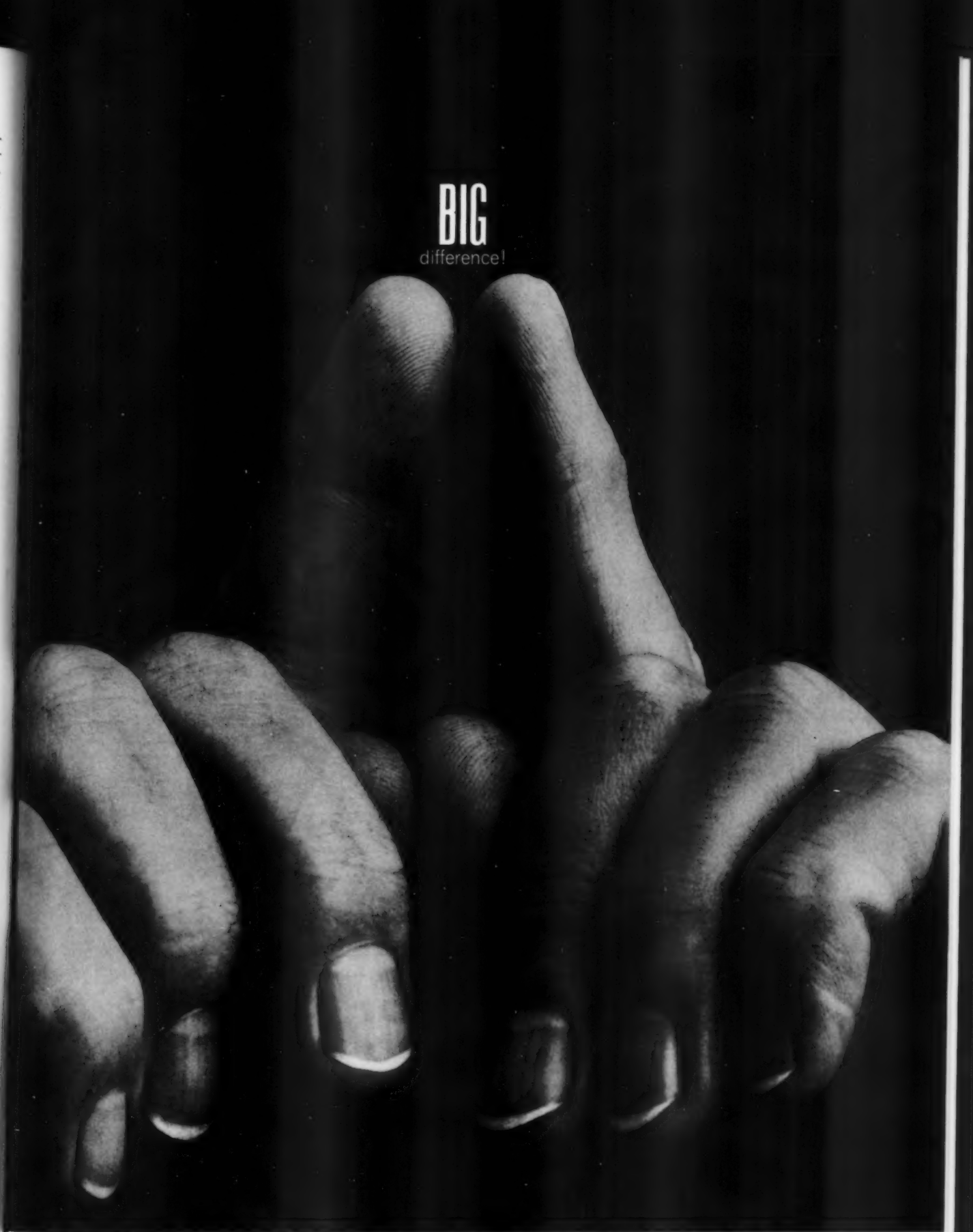

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American Perfumer
JUNE • 1961
VOLUME 76 No. 6

Synthesizing Chemicals and Biologicals by Microorganisms

BY OLDRICH K. SEBEK, Sc. D., Research Laboratories, The Upjohn Company, Kalamazoo, Michigan

IN 1959, THE ANTIBIOTICS for human and veterinary uses were valued at $366 million, for animal feed supplement, food preservation and crop spraying at $50 million. The total output of vitamins for the same year was worth $110 million and of steroid hormones $107 million.

The sales of certain organic acids, amino acids, solvents and mushrooms were smaller but nevertheless significant (1, 2). Since microorganisms play a major part in the manufacture of most of these materials, these data illustrate the economic importance of fermentation processes (a). They also illustrate the extent to which fermentations are at present used, especially in the production of certain pharmaceuticals and organic acids.

Fermentations are among the oldest chemical processes known to man. They were practiced to leaven bread and to prepare vinegar, wine and beer. To conduct these processes was an art enshrouded in mystery and handed down from generation to generation. With the increased scientific inquiry into the chemical and biological reactions, however, activities of various microbes were studied and clarified to a great degree.

During World War I and the ensuing years, industrial fermentation processes included the manufacture of alcohols (ethanol, butanol, acetone, glycerol), acids (lactic, citric), alcoholic beverages, and production of yeasts and of certain foods (bread, cheese, sauerkraut, pickles). Less than 30 years ago, and especially since the advent of antibiotics, large-scale fermentations underwent considerable changes and improvements. Microbes are now grown in tanks of many thousand gallon capacity under comparatively well controlled conditions, and aimed at economic production of desirable compounds. In recent years, continuous fermentation methods have been studied in an effort to increase the production efficiency. However, because of the complexities, both biological and technological, it is not likely that these techniques will be adopted by the industry in the near future.

With the exception of alcoholic beverages, alcohols are no longer the main fermentation products, since they are synthesized more economically from inexpensive petrochemicals. Instead, fermentation is at present the preferred, and in most cases the only route for the synthesis of larger organic molecules (antibiotics, some vitamins, industrial enzymes) and of certain organic acids. The microbiological preparation of the latter compounds is method of choice since their molecules and their preparations are sufficiently complex to resist economic chemical synthesis.

Because of their specificity, microbes are also called upon to modify intermediates employed for the synthesis of certain pharmaceuticals (steroid hormones, ascorbic acid, etc.) Essentially the same techniques are now used for growing animal cells, and for mass production of viral and bacterial vaccines. These successes stimulate lively research of the microbial activities and of new uses to which they can be put.

Fermentation processes employ enzymes, which are elaborated by microorganisms, to catalyze the formation of compounds of actual or potential importance to man. Success of this industry would not have been possible without basic knowledge in certain biological disciplines and engineering. Through the application of microbial genetics (mutation, selection), high yielding strains of actinomycetes, fungi, bacteria and yeasts have been developed.

Microbial physiology, enzymology and chemistry study and identify the intermediates and pathways through which the compounds in question are formed. When these intermediates are added into the fermentation media, the organism may incorporate them into the molecules of the final product without the

need of synthesizing them *de novo*. This method gives higher yields of the desired compound.

Similarly, the addition of analogues of such intermediates may yield analogues of the product. These techniques are used in the manufacture of antibiotics with notable success. Most of the enzymatic changes, through which the substrate is transformed into the product, take place inside the microbial cell. Therefore, the studies of mechanism of transporting these compounds through the cell wall, and an eventual elimination of this diffusion barrier, will have a definite impact on industrial fermentations.

There are other problems connected with a successful operation of fermentation processes: Continuous selection of new superior strains, their nutrition and maintenance, development of their resistance to the phage (virus) infections in the large-scale production, development of new media, suitable and reliable assays, chemical isolation and structure determination, pilot plant research on agitation and aeration, sterilization techniques, as well as automatic control of fermentation processes and equipment design. In addition, the production of pharmaceuticals calls for animal testing, for an evaluation of their curative and toxic properties, research on product formulation, sterile packaging and control testing.

1. Antibiotics

The spectacular success of antibiotics in the treatment of infectious diseases is among the greatest achievements in medicine. Although only some 20 years have passed since the discovery of chemotherapeutic properties of penicillin, the antibiotic production is one of the largest of all the fermentations. At present, around 20 antibiotics are produced industrially. Among them penicillin, dihydrostreptomycin (and streptomycin), and the so-called "broad spectrum" antibiotics (tetracycline, chlortetracycline, oxytetracycline and chloramphenicol ([b])) novobiocin and neomycin are most important.

These successes stimulate an intensive search especially in industry to uncover new ones active primarily against bacterial and fungal infections, and plant pathogens. In some places these preparations are tested to suppress selectively, the growth of viruses and various tumor cells. If these explorations are successful, antiviral and anticancerous agents will represent another important group of medicinals.

Since some of the established antibiotics (streptomycin, tetracyclines) have growth stimulating properties, improve the efficiency of converting feed to flesh, increase the hatchability of eggs, can reduce mortality and may have a sparing effect on vitamins and amino acids, they are also used in animal nutrition. But they can also have undesirable effects when fed at too high a level: growth inhibition, induction of biotin and vitamin B deficiencies.

Although many new antibiotics are described each year, they represent only a fraction of those which are discovered and abandoned for various reasons. For example, they are re-isolates ([c]) of known ones, inactive or toxic *in vivo*, or unstable. A therapeutically valuable antibiotic has to meet certain criteria: it has to be highly inhibitory to the disease-causing microbe and relatively non-toxic to the host tissue (a high therapeutic index); reasonably stable; well

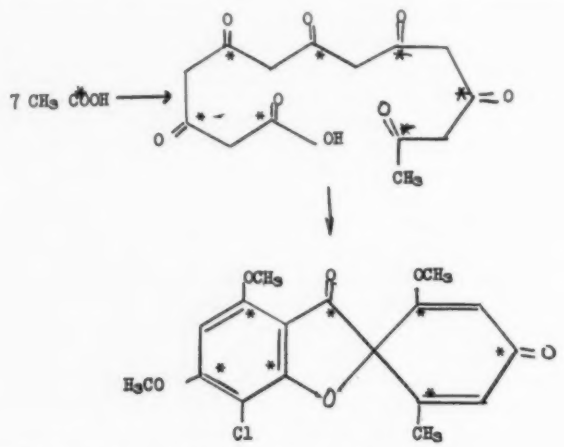


Fig. 1. Biosynthesis of Griseofulvin from Acetate

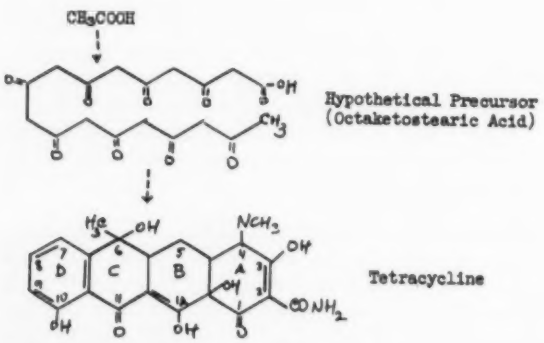


Fig. 2. A possible Biosynthesis of the Tetracyclines

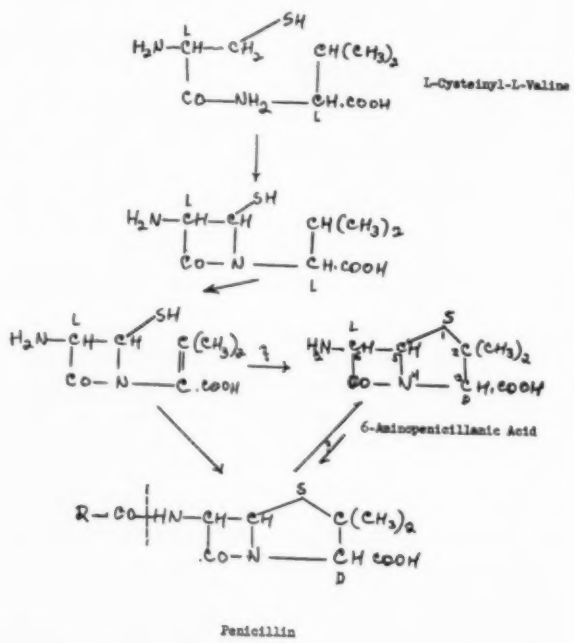


Fig. 3. Biosynthesis of Penicillin

absorbed when administered orally; well tolerated by the patient; and must not be inactivated by serum protein nor hemolyse blood.

Large-scale production is carried out in upright tanks of 25-50 thousand gallon capacity, well agitated and aerated. The fermentation media contain materials required for cell growth and precursors for the antibiotic synthesis (sugars, starch and grains, corn steep liquor, distillers solubles, animal stick liquor).

Although these antimicrobial agents exhibit a variety of novel structures, most of the well-known ones can be envisaged as being derived from the main metabolic pathways of the carbohydrate, protein, fat and purine metabolisms. Groups into which some of them belong, include oligopeptides (penicillin, cephalosporin N), oligosaccharides (streptomycin, neomycin), glycosides (novobiocin, hygromycin), nucleosides (puromycin, psicofuranine), macrolides (erythromycin, carbomycin) polyenes (amphothericins, nystatin). Yet, some clinically important antibiotics (tetracyclines, chloramphenicol) cannot be fitted into the known metabolic pathways.

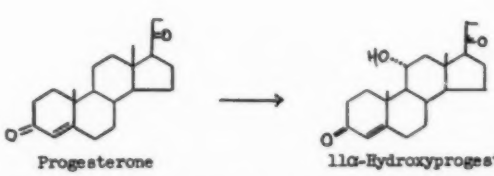
Acetate and amino acids, which have widespread functions in cellular metabolism, also represent common structural units of antibiotics. Thus, for example, griseofulvin, which is used systemically for the treatment of fungal infections, is probably synthesized exclusively from acetate units with the aid of a methyl donor, Figure 1.

It is possible that rings C, D and a part of ring B of tetracyclines are also formed from acetate, Figure 2.

The biosynthesis of penicillin, which has been studied most thoroughly, is outlined in Figure 3. Recently, the basic molecule of the antibiotic, 6-aminopenicillanic acid, was isolated as a fermentation product (3). While to date various penicillin derivatives have been prepared microbiologically, this discovery makes it now possible to tailor, or to completely synthesize, new penicillins chemically.

The antibiotics of the erythromycin group (macrolides) contain a large lactone ring, a ketone function and an amino sugar, and might be formed from poly-β-keto acids.

Acetate is also used for condensation to yield mevalonic acid, a precursor of the isoprenoid units which make up compounds of terpenoid structures (triterpenes and sterols). A few antibiotics (mycophenolic acid, helvolic acid, cephalosporin P) belong to this group.



Progesterone — 11α-Hydroxyprogesterone

Fig. 4. Microbiological Step (11α-Hydroxylation) in the Cortisone synthesis

2. Steroids

Since 1949, when a dramatic effect of cortisone—and later of hydrocortisone and other steroid hormones—in the treatment of rheumatoid arthritis was demonstrated, several operable but costly chemical processes for their production have been devised. A major problem was to introduce into the steroid molecule an oxygen atom at carbon atom 11 which is essential for the biological activity of such compounds.

While the introduction by chemical means was very difficult and inefficient, such operation was accomplished in 1952 (4) simply and in high yields by microbial means (Figure 4). The discovery of this reaction made it possible to work out economically feasible syntheses of cortical hormones and their derivatives. As a consequence, the sales of these compounds increased sharply from estimated $33 million in 1952 to $108 million in 1960. Their market prices were drastically reduced (for example, 1 g. of cortisone acetate was sold at $200 in 1949, at $16 in 1953, at $1.60 in 1961) which made these invaluable medicinals widely available.

Enzymatic studies on the mechanism of this hydroxylation revealed that the oxygen introduced into the steroid molecule originates from the atmospheric oxygen and not from water, and that the hydrogen is introduced through a direct replacement by a hydroxyl group (5, 6).

Through systematic screening many organisms were subsequently found which hydroxylate steroids at various sites. To date, practically all the available carbon atoms of the steroid molecule have been hydroxylated, (indicated by an asterisk in Figure 5)

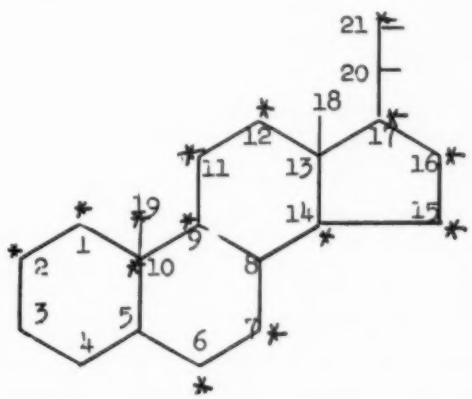


Fig. 5. Sites of Microbiological Hydroxylations

or other changes introduced (hydrogenation, dehydrogenation, epoxidation, lactonization, side chain degradation).

These changes were found to be carried out by fungi, bacteria, actinomycetes, yeasts, protozoa and algae but only the first three groups are used industrially. In most cases, the resulting compounds may then serve as intermediates for further chemical modifications.

The main effort in this area is to obtain steroids which are non-toxic, but highly active as anti-inflammatory, progestational, anabolic and hemostatic agents

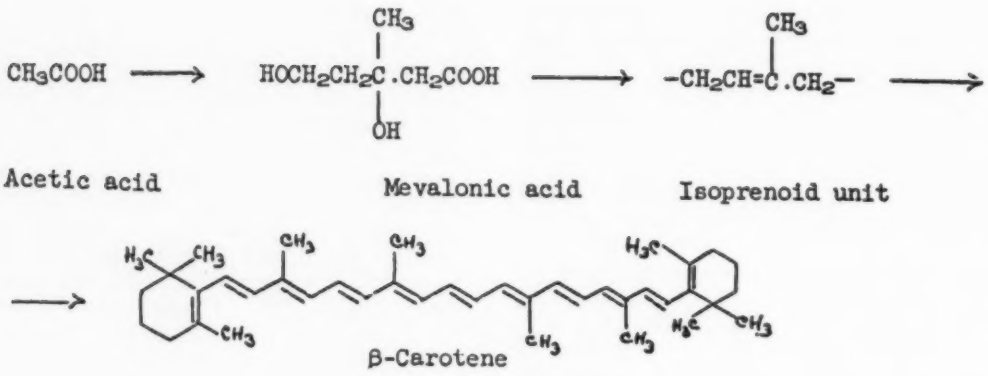


Fig. 6. Biosynthesis of β-Carotene

or used in anticancerous and cardiovascular treatments. Microbiological steps are included in the syntheses of several potent steroids, which dominate the market at present, viz., prednisone, prednisolone, 6α-methylprednisolone, 6α-fluoro- and 6α,9α-difluoroprednisolone, 16α-hydroxy-9α-fluoroprednisolone, 16α-methylprednisolone, 16α-methyl-9α-fluoroprednisolone.

The microbiological transformations of steroids are carried out by the same techniques and usually in the same equipment as employed for other microbial processes. The microbe is allowed to grow in submerged cultures with stirring and aeration, whereupon the steroid to be modified is added and the incubation is continued until the desired transformation has taken place. The steroid material is then extracted with a suitable solvent and, if necessary, purified by column chromatography and crystallization.

Although practically all the steroids used for the synthesis of steroid hormones are derived from plant sterols, selected strains of yeasts (*Saccharomyces cerevisiae*) which accumulate as much as 10% of ergosterol within their cells are potential sources of steroid hormones. However, because of their low cost, plant sterols are at present substrates of choice. Under ultraviolet irradiation ergosterol itself is converted to and marketed as vitamin D_2.

3. Vitamins

Although several vitamins (especially those of the B group) and provitamins are synthesized by microorganisms in varying amounts, at present only a few are manufactured—totally or in part—by microbial means.

a) Provitamin A (β-Carotene): Carotenoid pigments are synthesized by many bacteria, fungi, algae and by higher plants. One of the pigments, β-carotene, is of considerable importance in animal and human nutrition, since it is converted in the gut into vitamin

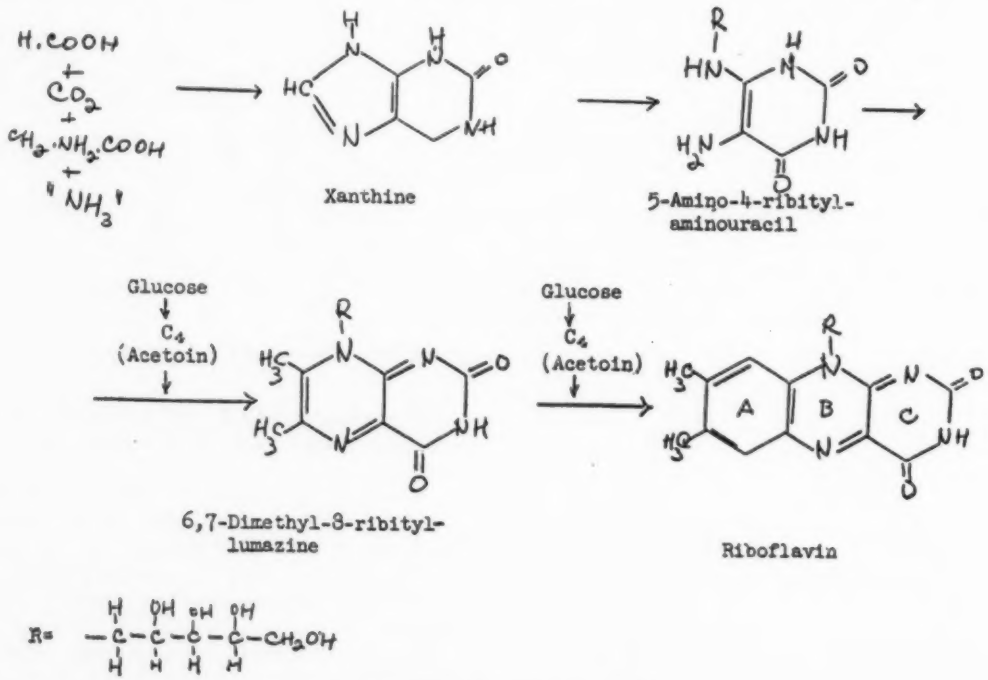


Fig. 7. Probable Biosynthesis of Riboflavin

A and, at the same time, provides harmless coloring matter for various foods. Practically all the β-carotene on the market today is made by chemical synthesis (or by extraction of plant material) and is quoted at 24¢/g.

An important observation made in 1956, namely that mixed plus and minus strains of *Choanephora cucurbitarum* grown together, produced 15-20 times more of the pigment than either strain alone (7). Subsequent development of this observation using new media and microorganism (*Blakeslea trispora*) resulted in still higher yields of the pigment. An inquiry into the biosynthesis of this pigment revealed that its basic precursor is acetic acid. With coenzyme A as a cofactor, this compound is converted into mevalonic acid (β-hydroxy-β-methyl-δ-valerolactone) and an active isoprenoid unit which is followed by a polycondensation, dehydrogenation and ring closures at both ends of the molecule to give β-carotene (Figure 6).

b) Vitamin B_2 (Riboflavin): Virtually all the riboflavin made in this country is synthesized microbiologically. In 1959, its production was 430,000 pounds. Its present market price is 3.6¢/g., while in 1938, when it was first introduced, it was sold at $17.50/g. Dried residues of the ethanol (yeasts) and particularly butanol-acetone (bacteria) fermentations contained significant quantities of riboflavin as well as of other vitamins of the B group. These residues are used for supplementing animal feeds. However, practically all of the marketed riboflavin is produced by two fungi, *Eremothecium ashbyii* and *Ashbya gossypii*.

Its formation by either culture is a highly aerobic process and a number of cheap natural materials and industrial wastes (wheat, flour, stillage, whey, corn-steep liquor, distillers solubles, animal stick liquor) are used for its synthesis. Yields of up to 2 mg. of riboflavin/ml. have been reported. Experiments designed to discover its biogenesis suggest that riboflavin is synthesized as a result of an excessive production of purines (adenine and guanine) which are normally required for the formation of nucleotides and nucleic acids. The reason for this suggestion is that rings B and C of the molecule have been found to arise from purines (which in turn are synthesized from formate, CO_2 and glycine).

Xanthine, which is formed in this way, is most probably metabolized to diaminouracil (or its ribose or ribitol derivative). The latter condenses with the ring A precursors (acetoin or diacetyl, and 6,7-dimethyllumazine) to yield the whole molecule of the vitamin (Figure 7).

c) Vitamin B_{12} (Cyanocobalamin): Vitamin B_{12} has become an important fermentation item since its discovery in 1948. It is synthesized by many organisms and obtained as a by-product in several antibiotic fermentations (streptomycin, neomycin, chlortetracycline, tyrothricin), from waste liquors of the acetone-butanol and ethanol fermentations, or from activated sewage sludge. In 1959, the production of all grades totalled 938 pounds which at $138/g. market price corresponded to $58.6 million worth of product. Its current price is $45/g.

For the processes, in which it represents a primary

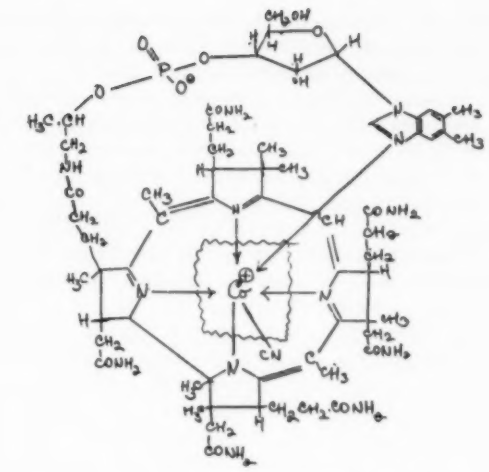


Fig. 8. Structures of Vitamin B_{12} and of Coenzyme B_{12}

fermentation product, several organisms are used. They are grown in agitated and aerated tanks containing molasses or glucose, distillers solubles and minute amounts of a cobalt salt. The production of the vitamin is completed within 6 hours (*Bacillus megaterium*) or 3-4 days (*Streptomyces olivaceus*). The yields amount to a few mcg. of the vitamin/ml.

The vitamin is stabilized by adjusting the fermented broth to pH 5, adding Na_2SO_3, and concentrated by evaporation. Highly purified preparations are used in the treatment of pernicious anemia and nutritional deficiencies in humans, but mainly for enrichment of animal feeds low in animal protein factor. As the work on this active material progressed, it became evident that several related types of this vitamin exist (cobamides). For illustration, Figure 8 shows the structure of vitamin B_{12}.

Its metabolically active form, coenzymB_{12}, contains no cyano group but has an adenine nucleoside, instead (8).

On the basis of this work it is now possible to prepare novel cobamides by supplying suitable precursors of the molecule to the growing cells.

d) Vitamin C (Ascorbic Acid): The microbiological step (sorbitol→sorbose) employed in the synthesis of this vitamin is described in Section 7.

4. Organic Acids

Large scale fermentation processes have been developed for the production of citric, lactic, fumaric, itaconic, gluconic, oxalic and acetic acids. Of these, only the first two are big fermentation items.

Although a small amount of *citric acid* is still extracted from citrus fruits, the acid is almost exclusively obtained by surface and, more recently, by submerged fermentations. In 1957, 65 million pounds of this acid were manufactured. The acid is used

primarily for carbonated beverages and in medicinals. Its salts and esters are used as plasticizers and chelating agents, sequestering agents for iron, especially for preventing the plugging of the oil wells. High fermentation yields of the acid are possible by the use of selected strains of *Aspergillus niger* which have to be maintained in a special way so that their high acid-producing ability is preserved. This, and high concentrations of low-cost molasses (which nevertheless must be treated to lower the Fe content) in the fermentation medium, and an efficient recovery of the acid account for the low price (30¢/lb.).

In spite of the fact that expanded uses for the acid have been found, no competitive chemical process has yet been discovered. Its biogenesis from glucose consists of several steps. It is believed that glucose is first cleaved into two C-3 fragments of which one of them is later decarboxylated (C-2), the other fragment is carboxylated (C-4). The condensation of the C-2 and C-4 fragments results in the formation of citric acid (Figure 9, Reference 9).

Lactic acid is produced by bacteria and molds almost exclusively from glucose or starch hydrolyzates. It is used in food and pharmaceutical industries as an acidulant and for various purposes in the chemical industry. Its production involves a symmetrical cleavage of the glucose molecule into 2 molecules of the acid. Its production in 1958 was 5.2 million pounds at the market price of 39¢/lb. Its current price is 29¢/lb.

The large scale production of itaconic acid by fungal fermentation is limited by a comparatively high cost of the product (38¢/lb.). Because of its easy polymerization and reactivity, the acid provides a suitable starting material for the preparation of resins and products of the methacrylic type, wetting agents, detergents and soil conditioners.

Microbiologically prepared fumaric acid has to compete with chemically produced maleic acid in most areas of its application.

Gluconic acid, another product of fungal (*Aspergillus*) and bacterial (*Acetobacter, Pseudomonas*) metabolism, is used in medicinals, foods and as sequesterant.

There are other acids synthesized microbiologically but new and expanded applications for them have yet to be found *viz.* kojic, α-ketoglutaric, oxalic, tartaric or gallic acids. **Ustilagic acid, produced by the corn smut fungus (*Ustilago zeae*) may be used for the preparation of macrocyclic musks in the perfume industry.**

5. Amino Acids

Until recently, all amino acids for human consumption have been derived entirely from plant and animal materials. Although their existence as excretion products in microbial cultures has been recognized for many decades, their amounts were so very small that no practical exploitation of these observations was ever attempted. In recent years, however, a new microbiological approach in Japan resulted in finding organisms and designing methods which yield several amino acids in substantial amounts.

Of considerable advantage is the fact that these acids are produced exclusively in their biologically active L-form. For this procedure the term "amino acid fermentation" has been coined. At present, L-glutamic acid and L-lysine are being manufactured by fermentation on a commercial scale in Japan and the United States. Favorable results have also been obtained with the production of L-ornithine (25 mg./ml.), L-valine (8 mg./ml.) and smaller amounts of L-alanine, and of L-tryptophan.

L-Glutamic acid has the largest commercial demand as a flavor enhancing agent (monosodium glutamate). One microbiological approach is based on the enzymatic transamination of α-ketoglutaric acid, or its reductive amination. From the industrial point of view, however, another process is superior. This process consists of a one-step microbiological operation in which *Micrococcus glutamicus* produces over 30 mg. of L-glutamic acid per ml. of medium containing glucose and ammonium salts. This high accumulation of the acid is the result of subtle physiological functions of biotin which is strictly required by the organism, and of an unusually high activity of L-glutamic acid dehydrogenase. A simplified pathway of L-glutamic acid synthesis is pictured in Figure 10, Reference 10.

L-Lysine and L-ornithine are also produced in a similar way by mutants of the same culture. Of these, L-lysine is of greater importance and is used as food supplement. It is also produced through a process which utilizes a L-lysine requiring mutant of *Escherichia coli*. The organism is grown under aerobic conditions in a glucose containing medium whereby 2, 6-diaminopimelic acid is formed. The cells are then disrupted with ammonia and the released diaminopimelic acid decarboxylase converts the acid to L-lysine under anaerobic conditions. These successes have stimulated considerable research in this area and more acids are expected to be biosynthesized in large amounts by the methods competitive with chemical syntheses.

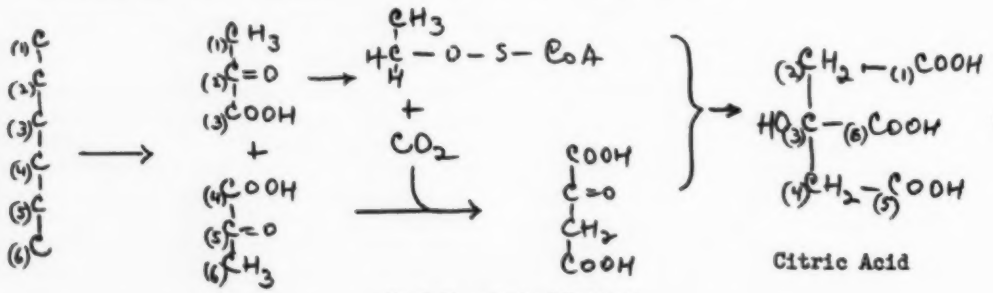


Fig. 9. Biosynthesis of Citric Acid

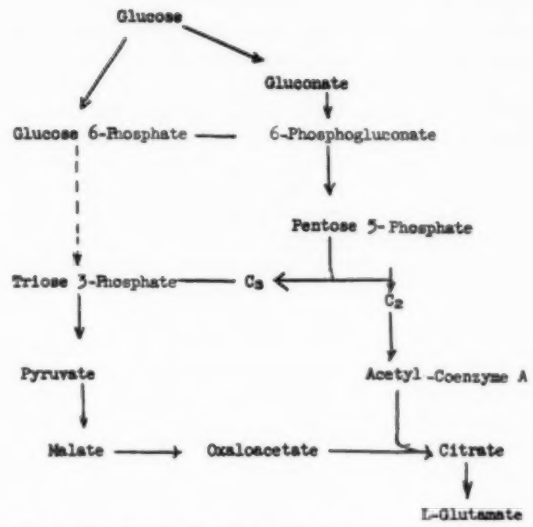


Fig. 10. Possible Biosynthesis of L-Glutamic Acid

6. Mushrooms

Mushrooms or fleshy fungi (*Basidiomycetes*) are used for foods and particularly for flavoring purposes, in soups and sauces. About 75 million pounds of edible mushrooms a year are produced in the U. S. alone with a total value at the farm of about $25 million. From their natural habitat, woods and fields, they have been taken indoors and are cultivated in special houses under controlled conditions. All the varieties cultivated in this country are those of *Agaricus bisporus*. Horse manure has been the only substrate used for mushroom growing. With the vanishing horse and only the riding stables providing all the available substrate for this purpose, synthetic compost was developed as a substitute (made of grasses, fodders, corn cobs and oat bulks with a definite nitrogen-carbon ratio). When mixed with horse manure, it gives mushroom crops comparable to those of natural substrates.

More recently, like other fermentation processes, the agaricus mushrooms have been cultivated in submerged cultures. Although nutritionally the same as the compost-grown mushrooms, these crops disappointingly enough lack completely the fresh mushroom flavor. However, the deep vat production of another mushroom (morel, *Morchella hortensis*) has been quite successful in this respect. The mushrooms are full-bodied, spherical nodules ¼ to 1 inch in diameter with the piquant morel flavor. They are produced within 3 days in up to 25,000 gallon fermentors (11).

Parenthetically it is of importance that lower fungi and other microorganisms (green algae) may supply in the future some of the essential nutritional needs of man in form of proteins and fats. Such attempts have been made during both World Wars in Germany. However, at present, these microbial products cannot compete economically with those of animal and vegetable origin, although their production is technologically feasible.

A consideration of this problem becomes more obvious when one realizes that some two-thirds of the world population today is underfed. With the high rate of population growth in the Far East and Latin America, and an average annual increase in the world of about 35 million people, greater food supply will be needed within the next 50 years. Fats and proteins of microbial origin may then represent a valuable contribution to this problem (12).

7. Alcohols and Solvents

The oldest and best known fermentations, the manufacture of beer, wine and distilled liquors, are based on the ability of yeasts to convert sugar to ethanol. Ethanol production by fermentation is steadily declining (it accounted for 30% of 200 million gallons produced in 1955) because of the increasing cost of molasses, the main substrate for the fermentation route. The decline is also caused by the increased production of ethylene, the key intermediate of ethanol synthesized chemically from petroleum.

The production of other alcohols and solvents (acetone, butanol and glycerol) by fermentation, which were of considerable importance 35-45 years ago, do not fare much better. In the last 15 years, there has been a continuous decline in their production. Of 540 million pounds of acetone produced in 1955, only 27 million pounds (5%) were prepared by fermentation. And yet, the acetone-butanol fermentation was of strategic importance during World War I, since this method provided the Allies with sufficient amounts of acetone vitally needed in the production of smokeless powder (cordite). Butanol was used as a solvent for lacquers.

Although the original culture used in the acetone-butanol process (*Clostridium acetobutylicium* [d]) utilized starch as a convenient substrate, strains have subsequently been developed which ferment molasses with equal efficiency. The fermentation is an anaerobic process and yields solvents in a definite ratio (butanol: acetone: ethanol 6:3:1). The solid residues, rich in riboflavin, and the respiratory CO_2 are valuable by-products.

Other selected clostridia ferment the same carbonaceous materials to mixtures of butanol and isopropanol, or acetone and ethanol, but again economic reasons make the production of these alcohols impractical.

During World War II, a considerable effort was spent on the bacterial preparations of 2,3-*butanediol* as an intermediate in the production of 1,3-butadiene used in the manufacture of synthetic rubber. Depending on the bacterium used, the diol can be produced in three stereoisomeric forms. Thus *Aerobacter aerogenes* and *Serratia marcescens* give mixtures of dextro- and meso, *Aeromonas hydrophila* a mixture of levo- and meso- and *Bacillus polymyxa* pure levoform. Although 47 g. of this diol can be produced from 100 g. of sucrose, this fermentation has never been carried out on a large scale because 1,3-butadiene is produced chemically from natural gas more cheaply than from 2,3-butadiene.

At present no glycerol is produced by fermentation.

Of considerable importance are the limited oxidative abilities of certain species of *Acetobacter* and *Pseudomonas*. By means of these organisms, primary and secondary alcohols are oxidized to their corre-

sponding aldehydic and carboxylic groups, and ketones respectively. Thus ethanol is oxidized to acetic acid; glucose to gluconic and 2- or 5- ketogluconic acids, disaccharides to their corresponding bionic acids; mannitol to fructose, 2,3-butanediol to acetoin, etc.

Quite recently, the production of dihydroxyacetone from glycerol by the action of *A. suboxydans* gained prominence. Dihydroxyacetone has been used in medicine to treat diabetes and in chemical syntheses. **Since it gives a suntan appearance when applied to the skin (a skin dye, reacts with the skin proteins), suntan lotions with this ingredient have achieved spectacular sales especially in summers marked by the lack of sunshine.**

The same organism is also used in the synthesis of ascorbic acid. Glucose, the starting material, is chemically hydrogenated to D-sorbitol, which is oxidized in high (20-30%) concentrations with *A. suboxydans* to L-sorbose in almost quantitative yields. This product is then chemically converted through four steps to l-ascorbic acid which in 1959 was produced in quantities of 4.9 million lbs. valued at $19.1 million. This efficient bacterial step in this process enabled the current market price of ascorbic acid to be $7/kilo.

8. Gibberellic Acid

This acid (and closely related gibberellins) has marked stimulating effect on the growth of many plants. It breaks the dormancy of seeds and tubers; accelerates the germination and emergence of seedlings in various plants; hastens the elongation of the stem internodes or flower formation. These striking but unrelated findings are results of detailed investigations of this compound which is a metabolic product of the fungus *Gibberella fujikurot* (°).

The structure for gibberellic acid is given in Figure 11. It is produced commercially in limited amounts by submerged fermentation and yields of 0.65 mg/ml. have been reported. Although the manufacture would present no problem, its large-scale production is limited by lack of major applications. Its growth enhancing properties are no inducement for its general use in U. S. agriculture because of considerable surpluses that already exist.

9. Polymers

Many microorganisms produce polymers particularly those composed of sugar units. One of them, a glucose polymer dextran of proper molecular weight (75,000 ± 25,000), can be used clinically as a blood plasma extender. Its synthesis is carried out by the bacterium *Leuconostoc mesenteroides* from sucrose either by direct fermentation or by cell-free preparation of dextransucrase. The resulting product is modified by partial hydrolysis, fractionation and purification. Although lately the interest in this product has been low, other sugar polymers have been synthesized by different organisms. They may compete with gums from natural sources and find applications as thickening, stabilizing or dispersing agents, in food processing, pharmaceutical, paper and other industries.

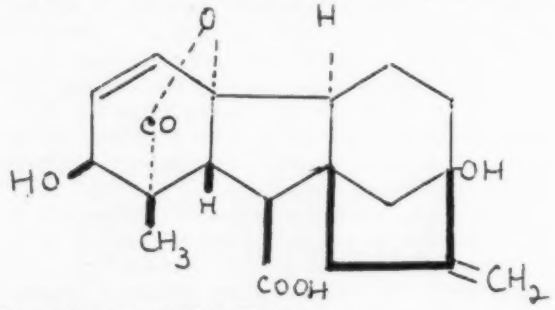


Fig. 11. Structure of Gibberellic Acid

10. Enzymes

The production of enzymes, which are used by several industries, is steadily increasing. Enzymatic preparations of varying purity find outlets in the production of alcohol to hydrolyze starch to fermentable sugars (amylase) in the textile industry for desizing the starch and gelatin- or casein- type sizings (mixtures of amylases and proteases);

for dehairing hides (keratinase and similar preparations);

in food industry to clarify fruit juices (pectolytic enzymes) and to prevent crystallization of less soluble sugars at high concentrations (lactase, invertase);

in the brewing industry to hydrolyze proteinaceous material causing turbidity in beer during cold storage (proteases).

Since all the fermentation reactions are enzymatic, the use of enzymatic preparations in such processes has considerable economic potentialities (*viz.* shortening of the fermentation cycles, no time delay in action because the cell-wall barrier has been removed, etc.). Research in this area is lively and will most certainly result in wider applications of the isolated enzyme preparations in established fermentations.

11. Microbial Insecticides

Certain bacteria are known to be pathogenic only for specific insects (13). One of these organisms, *Bacillus thuringiensis*, produces an endotoxin which is poisonous only for several noxious insects (Lepidoptera, such as the alfalfa caterpillar, the tobacco horn worm, the corn earworm, and the cotton bollworm). But, as ascertained by extensive field trials, it is harmless for other insects (bees), plants, animals and humans. The organism is grown on a commercial scale and applied on crops as a dust, sometimes mixed with bentonite or clay, or as a water spray. Although this is an attractive approach for insect eradication, preparations of other bacteria specifically pathogenic for certain insects, are not easy to develop (for example, *Bacillus popilliae*, pathogenic for the Japanese beetle).

12. Vaccines

The use of vaccines is one of the most important means of combating infectious diseases. In the manufacture of these biologicals, fermentation techniques are used but have to be modified to fit the nature of these organisms. The equipment has to be designed to prevent the destruction of essential ingredients during the sterilization, the dispersion of

infective aerosols or the loss of virulence and immunogenicity. Depending on the disease against which the protection is sought, three types of vaccines are generally used:

1. bacterial or viral suspensions which have been killed either chemically by antiseptics, by mild (56° C) heat or mechanically.
2. inactivated toxins (toxoids).
3. live vaccines (bacterial and viral).

For the preparation of killed vaccines from aerobic bacteria, virulent strains with closely similar antigenic properties are used. When the maximum growth has occurred, the bacteria are inactivated or killed, harvested by centrifugation and resuspended in a menstruum to a standardized strength. In this way vaccines against whooping cough, cholera, pertussis, typhoid fever, plague, anthrax, leptospira or swine erysipelas are made. When extracellular antigens are produced (diphtheria), the cell-free liquid containing the toxin is treated with formaldehyde to obtain the desired toxoid which may be further purified. Vaccines from anaerobic bacteria to combat gas gangrene, tetanus or botulinism are prepared in a similar way.

For the production of viral vaccines, either fertile chicken eggs or tissue cultures are used.

By the first method, vaccines against yellow fever, influenza, mumps, Newcastle disease, rabies or distemper, are prepared. Animal tissue cultures are grown for the production of vaccines against poliomyelitis, measles, hog cholera, and canine hepatitis. The large scale production of vaccines, especially of poliomyelitis in tissue cultures (monkey kidney) is based on the observations that

1. excised tissues of various origins can be grown in artificial media and support the multiplication of viruses;
2. bacterial infections of this delicate system can be prevented by the use of antibiotics;
3. that formaldehyde renders the virus non-infective but does not affect its antigenicity (14). Inactivation with formaldehyde is not used in the preparation of Sabin's live attenuated polio vaccine which is expected to be more effective and to impart longer-lasting immunity than Salk's formaldehyde-treated preparations.

13. Other Uses

There are other products of microbial activities which are of practical importance and interest:

salicylic acid formation from naphthalene;

methane production from sewage sludge for power and heating;

disposal of formaldehyde, carbolic acid, phenol, detergents (particularly of the alkylbenzene sulfonate type) and of other organic matter present in industrial waste liquors.

Microbes are used not only as inoculants for legume seed (to promote the nitrogen fixation from the air) or in the preparation of l-ephedrine, but also in oil prospecting or in extracting metals (copper, cobalt, nickel, tungsten or molybdenum) from low-grade ores by converting relatively insoluble sulfides (and oxides) to more soluble sulfates.

The successful growth of various mammalian tissues made possible large scale production of several vaccines. If suitable methods for cultivation of glandular tissues with their highly specialized functions are found, the synthesis of biologically and pharmacologically active compounds (hormones) by such systems will be possible.

In a similar vein, plant tissues, which are grown in large fermentors, may be used for the production of those chemicals which at present are elaborated only by the whole plant (sterols, alkaloids, essential oils, rubber, etc.). Finally, microbes may be used to maintain adequate living conditions for man's travels in space, since green algae *Chlorella* and *Scenedesmus* have been shown to provide sufficient quantities of photosynthetically produced oxygen with the concomitant utilization of respiratory carbon dioxide (15).

FOOTNOTES

(a) Originally, the term fermentation indicated the process whereby alcohol was formed from sugar. Pasteur used it to describe all the reactions by which microorganisms obtain energy in the absence of molecular oxygen. As the number of microbiological reactions and their products increased, these phenomena have been also referred to as fermentations, without regard to the original meaning of the word. For lack of a more descriptive term, the word fermentation is used here to describe anaerobic and aerobic dissimilations, simple chemical reactions and syntheses carried out by microorganisms. As the aim of this article is merely to make the reader aware of the importance which the microbes play in industrial operations, many details have been omitted.

(b) Although originally a microbial product, chloramphenicol is the only antibiotic made synthetically. This has been possible by elucidating its structure and designing an efficient chemical synthesis.

(c) The techniques used for the discovery of new antibiotics have changed considerably since the days of early screening, but the principles have changed very little.

(d) It is of historical interest that Chaim Weizman, the discoverer of this bacterium (1913) and developer of the process, was able to use this success to persuade the British Government to promise (Balfour Declaration of 1917) the creation of Israel which became a reality in 1948. Weizman became the first president of the new state.

(e) This microorganism is the etiological agent of the bakanae disease of rice and causes a rapid elongation of infected seedlings.

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BABY SHAMPOOS

BY H. S. MANNHEIMER, President,
The Miranol Chemical Company, Inc.

IT WAS AN ACCEPTED FACT that soap burnt in the eyes long before the existence of shampoos. It is also no surprise that soap shampoos and subsequently synthetic detergent shampoos caused eye sting. Still there is probably no one who ever washed his hair who has not been subjected on more than one occasion to one of the most annoying situations "soap in the eyes". Especially in the case of babies and children, murder most foul could not evoke louder and more desperate screams. Probably the fondest wish of any mother faced with hairwash hysterics was for a baby shampoo that could not burn when it got into the eyes.

There is, of course, very little reason why this type of shampoo should be confined only to babies. While it is not very likely that adults would scream the house down if an ordinary shampoo got into their eyes, the sensation can be most uncomfortable sometimes for hours afterwards. In view of the availability of non-eye stinging shampoos, the athletics and head gyrations required during hairwashing to prevent ordinary shampoos from getting into the eyes seem wholly unnecessary.

Eye sting vs. irritation

Strangely enough, a lack of eye sting in a surface active agent does not necessarily indicate that the agent is not an irritant. For instance, quaternary ammonium salts for the most part will not cause eye sting. However, such products which will give an adequate foam for shampoo purposes, if used in sufficient quantity to provide a shampoo, will cause not only severe irritation in the eyes but also may cause permanent opacity of the cornea in certain formulations. Therefore, it is clearly indicated that non-irritation of the eyes, and sting are two separate and distinct properties.

Non-irritation

In referring to non-irritation, it is pointed out that the description here is intended to mean true non-irritation and not permissible irritation in terms of the Draize Test which passes products not showing *remaining irritation* after 48-72 hours respectively. While this test is applicable also for true non-irritation, no irritation should be recorded at any time to deserve this description.

A very sizable group of new surface active agents (covered by 29 U. S. and additional foreign patents) was found which afforded the following requirements: Suitability for shampoo formulation, no eye irritation and no eye sting. All these products are salts consisting of an amphoteric and an anionic surface active agent of the sulfonate or sulfate type. This salt is formed in the following manner:

$$RX \qquad [(NY)_a \; R_2COOM]_b$$
$$\quad R_1 \; XS \; O_c$$

in which R & R_1 is a hydrocarbon group generally from C_8 to C_{18} or slightly larger if a benzene ring is included. They may be same or different.

X is hydrogen or any chemical group which affords a connection between R and the amine group(s) of the amphoteric or R_1 and the sulfo group of the anionic compound. They may be the same or different and are usually different.

Y indicates secondary tertiary or quaternary status of the amine nitrogen.

R_2 is a short hydrocarbon group which may be substituted.

M is an alkali metal salt.

a and b are integers of one or more and may be the same or different.

c is an integer denoting the number of oxygen atoms of the sulfo group.

From this general description it can be easily discerned that a fantastic number of these compounds can be prepared. By actual count those that have been claimed in the patent literature number over 300,000. It is obvious, of course, that these compounds would differ widely in their suitability for shampoo formulations. There are also differences in their irritating and eye sting properties. However, every one of those tested which proved suitable for shampoo formulations showed far less eye irritation than the most acceptable shampoo formulation made with con-

ventional surfactants. None produced eye sting in solutions of shampoo strength.

One of the quicker low cost irritation tests which gives excellent indications of what can be expected from the Draize Test is the intradermal skin injection test. This test is very severe because the test substance is injected under the surface of the skin.

This test can show irritation where even the Draize Test appears negative. For instance, even water will show a reaction. It is scored in the following manner:

−	No irritation
+	Slight reaction
++	Definite reaction
+++	Very definite reaction
++++	Very definite and spreading reaction

Water shows −/+ reaction. Olive oil castile shampoo, considered to be a standard of mildness shows ++ reaction.

In selecting amphoteric and anionic compounds for the salt formation, best results are achieved if products are selected whose irritation properties themselves are low. Obviously they must also possess physical properties suitable for shampoo formulations.

A modified cycloimidinium amphoteric (1) is such a salt.

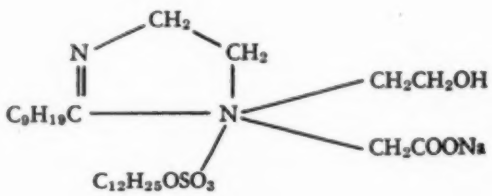

Figure 1

in which the amphoteric portion (2) is reacted with sodium lauryl sulfate as the anionic component. When formulated, as shown hereafter, this salt will not sting the eyes and gives an "o" score in the Draize Test and a "+" score in the intradermal injection test. It has copious, voluminous but somewhat open foam. Viscosity is low.

If the amphoteric starting compound is completely free from irritation, even better results can be obtained. One such compound (3) has a Draize score of "o" and a "-" score in the intradermal injection test. When reacted with Sodium Lauryl Sulfate Miranol 2MCA Modified is formed.

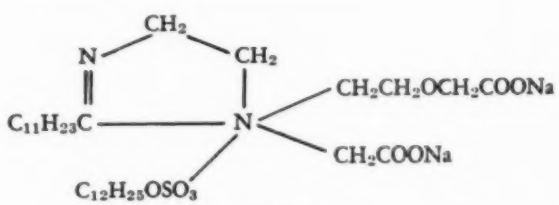

Figure 2

Like the modified amphoteric first mentioned (1), when properly formulated, it will not sting in the eyes, will have a "o" Draize score, but will be superior in the intradermal injection test with a "-" score. This is due to the fact that the starting product (3) had the same intradermal score. The shampoo produces a creamier foam than (1) and lends itself to the production of more viscous shampoos.

In formulating so called Baby Shampoos, it must be borne in mind that the possibilities of additives are limited if the non-stinging properties are to be preserved. Practically all compounds which are usually added to a shampoo to achieve various specific effects have eye stinging properties. Therefore, such compounds cannot be used at all or at best added in very minute quantities in order not to destroy the non-eye stinging effect.

Fortunately many additives are completely unnecessary. For instance, most of the modifying compounds are used for the purpose of achieving manageability, hair conditioning and wet combatability. All these properties are imparted to these shampoos through the amphoteric portion of these salts. As a matter of fact, these materials are used in a variety of nationally distributed shampoos to obtain these properties. For a rating of properties of surfactants in shampoos by panel testers see the publication of Powers and Fox, "The Role of Detergents in Shampoos" (4).

Miranol 2 MCA Modified or Miranol MSA Modified	30%
Hexylene Glycol	2%
Atlas G-7596J	1%
Perfume	(approximately 1/8%)
Water q.s	100%

The addition of 1-2% of a lauric superamide produces a more viscous formulation, but the higher the viscosity of the final product, the slower is the flash foam. Care must be exercised in the selection of the perfume because some are quite irritating. Hexylene glycol is a necessary part of the formulation and should not be omitted or substituted.

Due to the salt formation between the amphoteric and the anionic compound a very large molecule has been created. Its solubility in a small concentration of water is lower than that of a smaller molecule which results in slower development of flash foam in the absence of a water soluble solvent. Of all products tested which were free of objectionable odor or irritating qualities, hexylene glycol had the highest solvent power in the lowest concentrations. Atlas G-7596J contributes an extremely soft feeling to the skin after shampooing.

In conclusion, it would appear that new standards for non-irritation of skin and eyes in shampoos are required. Obviously as long as there were no products better than those causing at least a ++ rating for skin irritation in the intradermal injection test and eye irritation lasting up to two days, inclusive or corneal opacification (blindness), the best available had to be accepted. From the foregoing it is quite clear that this is no longer necessary.

References

1. Miranol MSA Modified.
2. Miranol SM Conc.
3. Miranol C2M Conc.
4. Powers, D. H., and Fox, D., J. Soc. Cosmetic Chemists, **10**, p. 116 (1959).

Significance of the Symposium

BY WILLIAM LAMBERT

THE DIFFICULT TASK of assembling a group of skilled, recognized authorities in the related fields of chemistry, physiology and psychology to give the results of their research on the highly specialized field of odor and olfaction at the annual symposium of the American Society of Perfumers was accomplished in an understandable and interesting way by the Symposium Committee.

The significance of the Symposium should not be underestimated for it brought to light and emphasized the scientific side of olfaction, an aspect that is too generally ignored by busy perfumers. While scientific data such as that presented is probably difficult for those engaged in purchasing or sales work who usually attend the meetings, from comments by some of them at the conclusion of the symposium, it was evident that the ideas of the speakers in a large measure were understood and created a favorable impression.

In the late twenties Col. Marston Taylor Bogert, professor of organic chemistry in Columbia University began a long range research project to investigate a possible relation between the graphical structure of the molecule and odor. It was financed by the American Manufacturers of Toilet Articles, predecessor of the Toilet Goods Association. Unfortunately funds were withdrawn after about a year. In that short time no important results were obtained.

Since then, other scientists have investigated the nature of odor and olfaction and various, more or less plausible, theories about both have been advanced. Odor and its probable incidence have been the subject of inquiry since the time of Titus Lucretius Carus in 47 B. C., as one of the speakers indicated. Like cancer which has been known to the medical profession since the time of Hippocrates, 460 B. C., and Galen, 131 B. C., the incidence of the dreaded disease still remains a problem to baffle scientists; but results of persistent research have contributed much that is useful in treating it.

In the same way, the basic work launched by the American Society of Perfumers may well have a profound effect on the future of the industry. By taking the first step as it did the Society recognized its stake and obligation to provide a forum for all manner of research to enlarge our understanding of the olfactory process. Perfumery is more than an abstract art. A fundamental grasp of its scientific aspects may well add to the dignity and skill of the professional perfumer and also advance the entire industry.

Seventh annual symposium

The American Society of Perfumers INC.

on: Experimental findings on odor & olfaction

President's Opening Address

BY HARRY A. CUTTLER, Revlon, Inc.

IN PREPARING FOR my address, it came as a great shock to suddenly realize that this is not the fifth, nor sixth, but rather the seventh annual symposium to be held by the American Society of Perfumers.

When I think of all the discussions, arguments, agonizing thoughts, momentous decisions, and soul searching that occur every year in order to prepare for this event, it becomes a "puzzlement" as to why we inflict such arduous labor upon ourselves. However, in retrospect, we find that because of our past symposiums we have been able to contribute in some measure to the understanding of what perfumery is about.

We have tried to clarify some misconceptions about the perfumer's work, and I hope that we have been able to enlighten those sections of the industry that encounter perfumery materials as to how we perfumers think, work, and communicate with each other.

I think we have shown—through our past symposiums—that a perfumer does not sit in an ivory tower divorced from the world, but is actually a hard working, down-to-earth composite of ⅖ artist, ⅖ scientist, and ⅕ *prima donna*. He has serious problems that still need enlightenment both in the artistic and scientific aspects of his field. He also has his deadlines, price considerations, and problems of quality just as any other professional with obligations toward the public. However, in the past, and to a great extent in the present, his work is still considered of a secretive nature. His problems, hopes, and desires are believed to be of no one's concern but his own, and it is thought that his success and failure depend solely upon himself and his artistic alter-ego. This is wrong.

The American Society of Perfumers has been striving to destroy these veils of secrecy and to reveal the perfumer for what he is . . . a hard-working professional with no magic at his command, dependent upon his fellow professional as well as the scientists, the trader and the public for the where-with-all to complete his masterpiece.

One of the ways this is being done is by means of the Society's Annual Symposium. It is for me a great source of pride that the Society of American Perfumers has grown from a mere handful to over 150 members in the 13 years of its existence. And it is an even greater source of pride that this group has not only raised the calibre and ethics of their profession to new heights, but has also given a platform for expression to those people, who are interested in the various phases of perfumery and olfaction, whether they be perfumers, chemists, businessmen, or biologists.

As president of the American Society of Perfumers, I am very glad to extend a welcome to all of you who have assembled here and look forward to seeing you again next year, the year after, and for many more years to come.

It now gives me great pleasure to introduce to you a person who has spent many years as a perfumer for one of our largest perfume houses; a man who has given unselfishly of both his time and ideas for the benefit of the American Society of Perfumers. And so, without further ado, allow me to introduce the man who conceived and worked for the symposium you are to hear, the Chairman of the Symposium Committee—Mr. Christian Wight.

Remarks by Symposium Chairman

CHRISTIAN F. WIGHT, International Flavors & Fragrances, Inc.

THE SYMPOSIUM CONCEIVED for this meeting had its origin in the feeling that there is scientific activity going on in various areas of olfaction to which we are paying little heed. All you will get here is a sample of the work going on in three separate and distinct areas. Perhaps because of its bewildering complexity, perhaps because of the difficulty of attack, few researchers have chosen to seek out the answers to the mechanisms of the olfactory process. The speakers have tackled the problem respectively from the behavioristic side, from the physiological side, and from the chemist's side—each of them seeking to expand the basis of our understanding of this atrophying function, the very one by which we as an industry, live.

Rarely indeed do imponderables fail to succumb to scientific attack, and I hope that this meeting will stimulate a more widespread support and participation, and that we go away awakened to the possibilities of progress with more serious effort by more people.

Our people have been preoccupied with achieving results by the old empiric methods and have ignored the prospects via the experimental route.

Each day we toilers in the vineyard make a hundred odor decisions hoping most of them are right.

Do we have any clue to knowledge of which conditions of temperature, humidity, mental attitude, state of physical tension or relaxation favors our acuity?

Do we apply the right techniques to group testing and know how to interpret their results, thereby gaining insight into the will of the public?

Do we know how to find and train a new generation of adept evaluators?

Do we know how to guide research into profitable channels?

Are we making full use of modern statistical methods and new instrumental equipment? I think not at all or not much.

If the academic pursuit of the "where" and the "how" and the "why" are not enough to generate enthusiasm, surely the commercial benefits of planned research, which would simplify our tasks and improve our results, ought to attract general support. One may remark that the recipient of the 1961 SCC Special Award, J. T. Davies, has contributed much to this field.

The disciplines of many sciences come into play in the search for understanding of what occurs when the human nose reacts to an odorant. The study of this miraculous instrument has been viewed by the medical profession as a part of the neurological system; by the biological chemist in terms of enzymes; by the physical chemist in terms of surface phenomena or absorption; and obliquely, by the psychologist in terms of registered impressions, associations, and motivations. Taste and smell straddle the middle ground between the subjective and objective and any plausible approach must be based on a combination of attacks by the anatomist; by the physiologist, as a property of chemical substance; as an interpretation by the psychologist of an integrated mental process. The drawback of a short meeting is, of course, inadequate coverage of so broad a field.

We have asked our moderator, Dr. William Amols, to present a little background covering the subject. Dr. Amols is a practicing neurologist on the staff of the Columbia Presbyterian Hospital as well as Assistant Professor of Neurology at the Neurological Institute. His extensive training in the neurological processes both in health and disease will serve him well to bridge the various sciences encompassed here. He has sandwiched a dozen hobbies into a life already rich and full, with a demanding medical practice, a teaching post and a heavy research schedule and now I think his inquiring mind has been thoroughly trapped by the challenge of the mysterious workings of odor perception. Don't suppose, though, that it is all blood, and sweat, and tears . . . they had Marilyn Monroe as a patient at the Institute a few weeks ago, and I bet everybody had to check her pulse! Before the Symposium, Dr. Amols and I were chatting about the great amount of ignorance that prevails about odor, and I said, "Dr. Amols, I imagine I could tell you all I know about olfaction in about five minutes." He said, "You don't talk very fast, do you? Never mind, between the two of us we know a lot about olfaction."

Basics of Olfaction

BY DR. WILLIAM AMOLS, Assistant Professor of Clinical Neurology, College of Physicians and Surgeons, Columbia University

I WOULD LIKE TO preface my remarks by explaining to you what a clinical neurologist like myself is doing here as the moderator of a panel of such distinguished authorities in the field of olfaction.

To the clinical neurologist the sense of smell is something that he usually forgets to test in the course of an otherwise thorough neurological examination. As a symptom of disease, smell is mentioned by his patients only to report its loss or more rarely its inappropriate unsolicited appearance, or its distortion. Olfaction is not, therefore, a very prominent fixture in the neurologist's work-a-day world.

Why, then, did I accept Mr. Wight's very kind invitation to appear before you? I did so because of some excellent advice, a learned friend and colleague of mine once gave me. He said that I should ask myself three questions before accepting any extra-curricular responsibilities. Can I contribute anything, can I learn anything, can I make anything? Well, I assure you I shall contribute nothing. Nor, with your very meagre budget shall I make anything. It must be therefore, that I expect to learn something and I am confident that I shall not be disappointed.

The sense of smell

The dictionary defines smell as the "property of a thing which effects the olfactory organ". Therefore it seems clear that smell is not exclusively the property of the substance being smelled, but that it depends in part on the existence of an intelligence of some sort to perceive it and to appreciate it. This is in contra-distinction to the other properties that a substance might have—its molecular weight, its solubility, its spatial arrangement of its component parts, etc. These properties exist whether or not someone takes the trouble to notice them.

Now this joint ownership of the property of smell, shared as it is between the smelled and the smeller, has created in the history of our culture, a difference in the emphasis that has been given to smell by man. In the very beginning of things this emphasis was most basic in the biological sense and was concerned largely with food-getting, with reproduction, and defense. To a certain extent this is still the case.

But in more recent times, with the establishment of a reasonably stable source of food, the relatively convenient availability of a mate, and the delegated responsibilities of defense, smell has come to play an increasingly subjective role reflecting more the esthetic refinements of sensation made possible by security and leisure. Hence, the many references to frankincense and myrrh and to the perfumes of Araby.

But in most recent times, in this age of reason and examination into the fundamental nature of things, the emphasis has once again become basic; but now in the bio-chemical rather than the biological sense, and in the physiological and psychological senses, as well. Now it would seem that our preoccupation seems to be less with the luxurious and sybaritic enjoyment of odor and aroma than with our understanding of the mechanisms of olfaction.

One cannot help but wonder a bit sadly and perhaps wistfully whether in poking about with this bright light of scientific investigation, we aren't run-

ning the risk of losing something of the mystery and romance of sensual experience. But then I don't suppose we need worry too much, when we have only to reflect on how successfully this business of smell has thus far eluded our most searching efforts to find it out.

Since *We* seem to be living in this most recent of times, we are all here involved in the substitution of the cerebral for the autonomic approach to the phenomenon of smell. You will notice that when I mentioned that our emphasis on smell had once again become basic, I pointed out that this was no longer so in the biological sense, but in the bio-chemical, the physiological, and the psychological senses instead. It is therefore not mere happenstance that our panel is composed of a bio-chemist, a physiologist, and a psychologist. (As for myself, I think you can tell from the tenor of my remarks thus far that I perhaps represent the sixteenth century.) This confluence of specialized disciplines is as it should be; for if the dictionary is correct, and smell belongs jointly to the smelled and to the smeller, then obviously both must be carefully studied if the puzzle of olfaction is ever to be understood.

Sense of smell puzzling

And a puzzle it continues to be. For although smell is one of the most primitive of senses, emerging long before vision and audition, we still feel less secure of our information concerning smell than we do about sight and sound. At least in the case of the latter, the input stimulus, no matter how elaborate in its final evolution, is still reducible to variations on the basic components of frequency and amplitude of wave form. Unfortunately, nothing so gratifyingly basic has yet been irrefutably put forth for smell. There seem to be almost as many odors as there are odorants and perhaps as many special receptors. Possibly from today's symposium will come some sort of unified field theory which will change all this.

Volatility is common tenet

Of the many theories of olfaction that have been elaborated over the years—and there are perhaps some thirty or more of these—only one tenet has been common to them all. And that is, to be odorous, a substance must be volatile. What happens when the volatile molecule reaches the olfactory mucosa is still something of a mystery. Does solubility—particularly lipoid solubility—have something to do with its ability to activate the olfactory receptor? Probably so. But not all fat soluble volatile substances are odorous. Does this mean that they might be odorous for some species if not for man? Possibly so. If not, does it mean that in addition to solubility, the configuration of the molecule plays a role? Again, quite possibly so, for stereo-isomers may have different odors and the slightest change in structure can convert an odorant into a non-odorant.

Current theories of olfaction are quite taken with this lock and key type of thinking in terms of molecular structure and sight activation, whether it be by penetrants (or puncturing), or by patterned absorption. But one wonders how truly "current" such a theory can be when he reads the words of Titus Lucretius Carus written in the year 47 B.C. *You cannot suppose that atoms of the same shape are entering our nostrils when stinking corpses are roasting or when the stage is freshly sprinkled with saffron of Cilicia and a nearby altar exhales the perfumes of the Orient.—You may readily infer that such substances as agreeably titillate the senses are composed of smooth round atoms. Those that seem bitter and harsh are more tightly compacted of hooked particles and accordingly tear their way into our senses and rend our bodies by their inroads.*

These words were written over 2000 years ago. It is almost as though Lucretius had anticipated the sort of data that modern techniques have made available.

Another unique aspect

If, indeed, it is true that odor is a function of molecular structure, that there are as many odors as there are appropriately structured molecules, and that each such molecule is capable of imparting its own characteristic and identifiable odor to the brain, then the sense of smell seems to be unique in yet another respect. This is: much, if not all of the discriminatory aspects of smell are carried out in the end-organ receptor, and are conveyed to the brain only for the purposes of integration with other sense-information, for storage as memory, and for recall and communication. Such a concept seems almost disrespectful to the complexity of the brain. But may be permissible when one remembers that there was smell in a highly evolved form long before there was a brain—at least in the sense that we like to think of the brain.

Emotion plays a role

Indeed, that portion of the brain that deals with odor is recognizably different from the more recently acquired cerebral mantle. It is known (or believed) to be more intimately concerned with that inner function called "emotion" as opposed to thought—in the ideational, pictorial, or symbolic sense. It is almost as though emotion is the "consciousness" of olfaction in the manner that "thinking" is the consciousness of the other senses. Certainly it is common experience that the emotional evocations of odor are stronger than they are for sight and sound!

If so, this would tend to complicate the conventional psychological approach to the study of olfaction and would make one wonder whether a subject's responses in terms of verbal or written communication constitute an accurate index of his discriminatory capacities.

Now all this that I have said is really in the nature of a query. As I said at the outset, I myself have nothing to contribute, but have much to learn. In the interest, then, of information, as opposed to speculation, I will conclude these introductory remarks and yield to the first scientific paper of the symposium.

Identification of Odors

BY DR. TRYGG ENGEN, Associate Professor of Psychology, Brown University, Providence, R. I.

THE UNDERSTANDING OF ODOR involves the physiology of the olfactory system and control and measurement of the chemical agents which stimulate this system. However, odor would hardly be a problem unless there were human observers to report on olfactory experiences; thus we regard the psychology of odor as the central problem.

The way in which a person adjusts to his environment depends on how well he can perceive his social and physical environment. The problem for the psychologist, then, is to measure these perceptions. No physical instrument can do this. The psychologist therefore must use the human observer as a meter. Michels, a physicist, and Helson, a psychologist, in discussing this problem state that: "The signal supplied to a meter is exactly analogous to the stimulus to which the human reacts. The ordinary meter yields its measurement in terms of a pointer reading, the human meter indicates the magnitude of the stimulus by some sort of a motor or verbal response" (9).

Psychophysics of odor

The interest of the psychologist in the odor problem is primarily in the psychophysics of odor; that is, in the relationship between the physical characteristics of an odor stimulus (e.g., concentration dilution values) and the verbal judgment of the corresponding subjective experience (e.g., presence or absence of odor). Such psychophysical relationships have been extensively studied, especially in hearing and vision, and it has been demonstrated that such subjective dimensions can be measured with good reliability.

Although relatively little research has been undertaken so far in olfaction, progress has been made in adapting such measurement methods to olfactory psychophysics. Much of this work has been concerned with the method of presenting the odor stimulus which the observer is required to judge. The results have indicated that the method of sniffing (as compared with blast injection technique) is the most satisfactory and that reliable results can be obtained for both intensity and quality of odors (e.g., 7, 11).

With this knowledge, it is possible to carry out further research on the judgment of odor with procedures which have been successful in other sense modalities. This paper will be concerned with the application of information theory and concepts in evaluating the ability of the human observer to discriminate and transmit information about physical stimuli. Basically, the problem is to estimate the number of classes of stimuli (e.g., intensity levels of a tone or odor) that can be discriminated without error when they are presented singly. It has been estimated that this number is 5 for loudness and pitch and 3 for taste, for example (10). It is the purpose of this paper to report the results of experiments conducted by Pfaffmann and the author (3, 4) concerned with the ability of unpracticed observers to identify odor intensities and qualities.

These experiments were concerned with the following specific questions:

(a) What is the greatest number of different intensities of an odor an observer can learn to discriminate and then identify correctly by rank-order or label? How does this number compare with the number of different odor qualities he can identify without error? There has been much speculation about the difference between intensity and quality, but apparently no experimental analysis has ever been undertaken.

(b) How is the accuracy of these identifications or absolute judgments influenced by the selection of odorants, size of step between stimuli, concentration value of stimuli, practice, and the number of stimulus categories presented to the observer? It is important to measure the effect of these variables, because they are significant in other sense modalities.

Method

The Observer. Judgments were obtained from groups of about five college students. The observers were paid at the usual student rate of $1.00 per hour. None of them had any previous experience in psychophysical experiments.

Testing Room. The experiments were performed in a 5′ x 7′ room which was well-ventilated and air-conditioned. The temperature of the room was kept at 70°F. and humidity at 50%.

Procedure for Intensity Judgments. The intensity experiments were conducted with amyl acetate, n-heptanal, n-heptane and, phenylethyl alcohol. The stimuli were prepared according to a procedure suggested by Beck, Kruger, and Calabresi (2). Mallinkrodt's Benzyl Benzoate (USP XIII, 387 control TSN-1) was used as a dilutent. The dilutent and the odorant were mixed in a 10 x 75 mm. test tube with a pipette.

The dilution series was geometric such that stimulus #1 of the series contained 100% of the odorant; stimulus #2 contained 50% of the odorant and 50%

The research on which this paper is based was supported by a grant from the General Foods Corporation and was conducted in collaboration with Professor Carl Pfaffmann.

of the dilutent; stimulus #3 contained 25% of the odorant and 75% of the dilutent, etc. Thus, each stimulus contained half as much of the odorant as the preceding one of the series. The total amount in the test tube was 1 cc. The test tube was stoppered with an aluminum wrapped cork, which was removed only for sniffing. The dilution series were renewed frequently.

In the first part of the experiment the observer learned to identify a certain number of stimulus intensities, and this part of the procedure was repeated at the beginning of each day. A rack with five stimuli, rank ordered from strong to weak, were presented to the observer, and he was instructed to learn the correct position of each so that he could identify it when later it was presented singly. The observer would then sniff the content of each test tube, compare it with the others. He was allowed to continue this until he was satisfied no improvement would result from further practice. The stimulus rack was then returned to the experimenter behind a screen where it could not be seen by the observer.

Next each of these five stimuli was presented singly in a random sequence, and the observer was now instructed to identify its rank order in intensity among the five stimuli; that is, the observer was required to make absolute judgments of stimulus intensity. There was never any restriction on the time allowed for a judgment. Each stimulus was presented 50 times for a total of 250 judgments of a set of five stimuli.

A correction procedure was used such that the correct rank order was indicated by the experimenter after the observer had made his judgment. After a period of about 12 min. the observer was given a rest while one or two other observers were run in a similar manner. Each observer thus worked and rested for about three hours per day three to four days per week. The first two days were used for practice, and an effort was made to schedule each observer at the same time of the day. The observers were asked not to use perfume on days they served in the experiment and not to eat or smoke an hour before an experimental session.

Table 1

CHEMICAL AGENTS USED IN THE EXPERIMENTS

Different	Similar	YM
Acetanisol	Acetate C-8	
Acetic acid	Acetate C-9	
Acetone	Acetate C-10	
Amyl acetate	Acetate C-11	
Allyl Caproate	Aldehyde C-7	
Benzaldehyde N.F.	Aldehyde C-8	
Benzene	Aldehyde C-10	
Benzyl Cinnamate	Aldehyde C-14 (peach)	
N. Butanol	Aldehyde C-14 (pure)	
N. Butyric acid	Aldehyde C-16	
Camphor (lt. syn.)	Aldehyde C-18	
N. Caprylic	Allyl Caproate	
Citral	Amyl acetate	
Clove oil	Amyl Phenylacetate	
Coumarin	Amyl Propionate	
Diacetone alcohol	Benzyl Acetate Coeur	
Ethyl acetate	Benzyl Butyrate	
Eugenol	Cinnamyl acetate	
Guaiacol	Cinnamyl Butyrate	
Heptanol	Cinnamyl Propionate	
Heptane	Citral	
Hexane, N.	Citronellyl acetate	
Indol	Citronellyl Butyrate	
Isopropanol	Dimethyl Anthranilate	
Linalool	Geranyl Butyrate	
Menthol	Geranyl Propionate	
Methanol	Linalool	
Methyl Salicylate	Menthol	
Musk	Methyl Anthranilate Standard	
Novoviol, alpha	Methyl Salicylate	
Phenylethyl alcohol	Phenylethyl acetate	
Pyridine	Phenylethyl alcohol	
Safrole	Phenylethyl Isovalerate	
Vanillin	Raspberry aldehyde	
Butyl acetate	Tolyl acetate	
Nitrobenzene	Vanillin	

Procedure for Quality Judgments. The procedure was similar to that followed for intensity judgments. The two sets of odor stimuli used are listed in Table 1. The set of so-called different odor stimuli was selected to sample a variety of odors, e.g., fragrant, spicy, fruity, burnt, etc., and the similar set was selected to sample only sweet-fruity odors. When fewer than 36 odorants were used in an experiment, they were selected at random from among one of these two sets. This will become clearer below.

In this case the observer was asked to label each of the odor stimuli with his own association to that odor, thus avoiding the restriction of an arbitrary response code. When labels had been determined and checked a second time to avoid duplications, the observers were required to identify each odor stimulus presented one at a time with the previously assigned label.

In other respects the experimental procedure and data analysis were the same as for intensity judgments.

Analysis of Data. The observers in these experiments were making what are called absolute judgments. Such judgments lend themselves to information analysis adopted in psychology from communication engineering. Garner and Hake (6) have shown that such analysis of absolute judgments yields a measure of the accuracy with which an observer can judge which of a set of alternative stimuli occurred at any specified time. In other words, this measure gives an indication of the largest number of stimuli the observer can judge in this manner without error.

(Information can be defined in the present case as the logarithm to the base two of the number of stimulus alternatives being judged.) The unit of this measurement, the bit (for binary digit), specifies the number of two-choice judgments which must be made to identify which one of several alternative stimuli is presented at the moment.

For example, if a set of four stimuli is used and one is presented singly and at random, the observer must first decide from which of two groups of two stimuli it is and then which one of these two stimuli it is. If he makes no errors in identification the observer is transmitting 2.00 bits of information. If eight stimuli are presented in this manner, he is making three two-choice judgments; that is, he is transmitting 3.00 bits of information. Mathematically this can be expressed as $I = \log_2 1/p = -\log_2 p$, where I is bits/stimulus and p is the probability of occurrence of each stimulus (1/8 or .125 in the last example). Thus, $I = \log_2 1/p = -\log_2 p = 3.00$.

The psychologist of course is not interested in the particular stimulus or "message" but in the average amount of information expected from the observer or "source." Therefore, he computes an average amount of information the observer can transmit per stimulus,

weighted in terms of the probability of occurrence of each stimulus, according to the formula $I = \Sigma p' \log_2 1/p - \Sigma p' \log_2 p' = -\Sigma p' \log_2 p'$. The anti-logarithm of the results may be used as a measure of the number of stimuli that the observer can discriminate absolutely.

The maximum amount of information transmitted is limited by the number of alternative stimuli used, and the larger the number of incorrect judgments, the larger the term subtracted from this quantity. For our purposes it is convenient to talk about information rather than errors for this permits a more direct comparison of the observer's ability to identify intensities vs. qualities as well as olfaction vs. the others sense modalities.

Results and discussion

Intensity Judgments. In Table 2 are presented the results from the first experiments on absolute judgments of intensity and quality. We shall first consider the intensity judgments which were obtained with four odor stimuli, amyl acetate, n-heptanal, n-heptane, and phenyl-ethyl alcohol, in dilution series of 100, 50, 25, 12.5, and 6.25%. Judgments were obtained with four and five observers.

The results indicate that an observer with a minimum of practice is able to transmit about 1.5 bits (i.e., three categories) about intensity differences in odor. The S.D.'s of the means give a rough indication of the relatively large individual differences. These results are in close agreement with those obtained for taste with salt or sucrose solution differences, but somewhat lower than those obtained for auditory and visual stimuli (10) when these varied in only one dimension.

It can be concluded on the basis of these findings that taste and odor intensities appear to be somewhat less distinctive than, for example, auditory intensity differences. Whereas in audition an average observer can learn to discriminate and remember, at least over a short period of time, about five different stimulus categories. The average appears to be approximately three for taste and odor.

Table 2

Average amount of information in bits obtained for five alternative stimuli with 100, 50, 25, 12.5, and 6.25% dilution concentration values, for each of four odorants

Odorant	N	Mean	SD
Amyl acetate	5	1.52	.37
n-Heptanal	4[a]	1.53	.16
n-Heptane	5	1.51	.33
Phenylethyl alcohol	5	1.58	.27

[a] One woman became nauseated from this odorant and testing had to be discontinued.

It should be recalled here that our observers had no previous experience in odor identification. It would indeed be interesting to repeat these experiments with perfumers as observers. However, you will see that we did obtain some data on the effect of practice which are relevant to this problem.

The problem now becomes one of determining how these results might vary with the sample of odorants and concentration characteristics of the odor stimuli. As far as the intensity judgments are concerned, Table 2 indicates that no reliable differences were obtained with four different odorants. It is not possible, of course, to conclude that a reliable intensity difference cannot be obtained with the information measure between *any* odorants, and we shall come back to this point with respect to quality differences. However, preliminary work with several other odorants indicates that such intensity differences, if any, would be very small. It appears that intensity differences between odorants will be more apparent in subjective threshold concentrations.

However, as one would expect from the knowledge of psychophysical judgments, the concentration value and size step between the stimuli had a significant effect on the amount of information transmitted. To measure these variables 12 sets of five stimuli were prepared by using three dilution series of each of the four odorants described above, namely, 100, 50, 25, 12.5, and 6.25%, 3.12, 1.56, .78, .39, and .20%, and 100, 25, 6.25, 1.56, and .39%. The 12 sets were assigned at random to each of three observers yielding a good distribution of odorant, size step, and concentration value throughout the experiment. The results were as follows:

1. The observer is less likely to confuse strong stimuli (high concentration values) than weak stimuli. That is, the stimulus set consisting of 100, 50, 25, 12.5, and 6.25% solution of the odorants were judged more accurately than the stimulus set consisting of 3.12, 1.56, .78, .39, and .20% solutions of the same odorants.

2. There are also differences in accuracy of identification related to the size of the step between the stimuli. Thus the stimulus set consisting of 100, 25, 6.25, 1.56, and .39% solutions of the odorants yielded better results, than both of the series described above. Figure 1 presents these results in terms of percentum correct judgments of each stimulus in the three series.

The first experiments (Table 2) had given indication of practice effects; that is, improvement in accuracy over trials. The 12 sets of stimuli in the experiment above were randomized to measure the

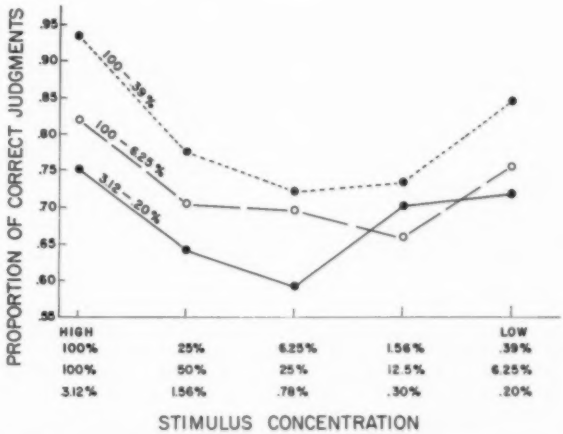

Fig. 1. Proportion of correct absolute judgments by three observers of odor intensity as a function of the position of the stimulus in the series, size of step, and concentration dilution value.

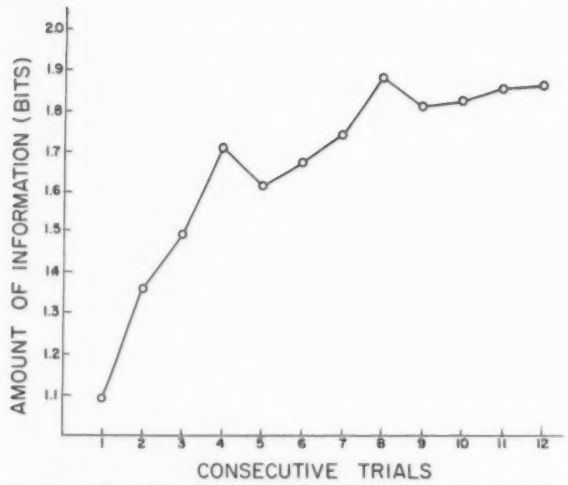

Fig. 2. Practice effects on absolute judgments of odor intensity measured by amount of information transmitted in 12 consecutive trials by three observers. Each trial is on a different set of five stimuli.

effect of practice and to balance out odorant, size step, and concentration value. The group results presented in Figure 2 show that the observers' performance shows improvement up to the eight sessions where it levels off at about 1.85 bits per stimulus or close to four categories. This experiment required seven weeks of work.

These practice results are averages for the group, and the best observer reached nearly perfect performance on five stimuli. To assess "maximum channel capacity," (1) or the best possible performance possible under optimum conditions, and the degree to which such performance may depend on "input information," (that is, the number of stimulus categories presented for judgment) this well-practiced "expert" observer was presented, consecutively, 3, 5, 7, 10, and 13 stimulus categories of amyl acetate in 50% steps under the same instructions previously described. The results (given in Figure 3) show that whereas the judgment efficiency is nearly 100% up to 5 alternative stimuli, no appreciable improvement results from presenting more than five stimuli. Also efficiency is greatly reduced as shown by discrepancy between input and output information.

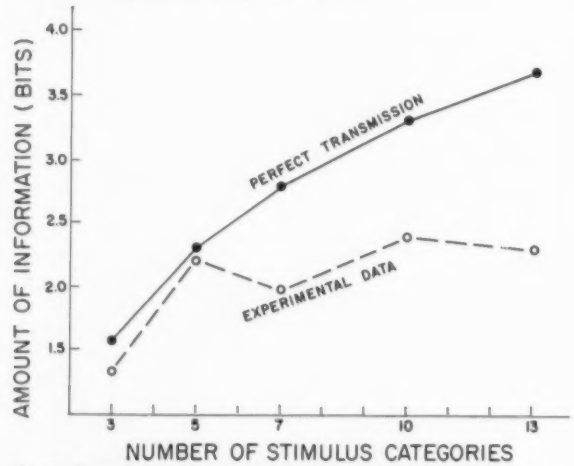

Fig. 3. Amount of information transmitted about odor intensity by a well-practiced observer as a function of the number of stimulus categories presented for judgment.

Quality Judgments. The human observer's ability to identify odor intensities has often been contrasted with his ability to identify different odor qualities. The results from the first quality experiments from five observers are presented in Table 3.

1. By opinion polling in a large undergraduate class, it was determined that a 6.25% solution of amyl acetate was, on the average, judged to be of medium intensity.

2. This amyl acetate solution was matched with 23 other odor stimuli selected from the 36 different odors in Table 1. A dilution series was prepared as above for each of these twenty-three odor stimuli, and these dilution series were presented to each observer in a random order. For each odor stimulus, the observer was required to select the test tube which contained an odor intensity equal to that of the 6.25% amyl acetate. This experiment yielded 24 odor stimuli of subjectively equal and medium intensity but of different qualities. The same 24 odor stimuli, but each in a 100% solution, were presented for a second series of judgments. A third selection of 24 odor stimuli was made from the 36 similar odors in Table 1, each of these also being presented in 100% solutions.

Table 3

Means and SDs of bits of information transmitted by 5 Ss for various samples of odorants

Sample of Odorant	Mean	SD
Different odorants of equal and medium intensity	4.00	.17
Different odorants unequal intensities	4.03	.19
Similar odorants unequal intensities	3.86	.43

The results indicate that the average observer could transmit about 4.00 bits of information about quality; that is, he could use about 16 categories (the antilog of 4.00). The results did not vary appreciably with the intensity of these odor stimuli, because the matched stimuli of medium intensity yielded about the same result (4.00) as when they were unmatched (4.03).

However, the kind of quality seems to be somewhat important, because when all the odor stimuli were relatively similar (sweet-fruity) rather than varied, the amount of information transmitted decreased to 3.86 (or 14 categories). The results for quality are similar to those obtained for tones when they are varied both in frequency and amplitude (10).

No evidence of practice effect was observed in the case of the judgment of quality. Perhaps this differential effect of practice on intensity and quality tells us something about our observers' familiarity with odors. The ability to identify odor quality is usually more practiced in everyday activities than the ability to identify various intensities of the same odor. One might expect improvement after a longer training period than possible in the present experiments. In 1926 Free (5), in an article entitled "Shall we train our noses?" reported on some experiments similar to the present ones and concluded: "The classes of the community who have (in our tests) the best aver-

ages of smell recognition are the pharmacists and the chemists; which is quite natural, since the handling of drugs and chemicals gives continual and insistent practice to the smell-recognizing centers of the brain. Are druggists therefore happier than other folk; less bothered by bad smells, more appreciative of good ones? It is quite possible that they are. Someone ought to find out." I leave it to you to carry out the last suggestion!

The next experiment evaluated the information transmitted when both qualities and intensities of each odorant varied in the sample presented for judgment. Sixteen different odor stimuli were used, each in three concentration dilution values of 100, 25, and 6.25%. The purpose of this experiment was to determine whether or not the information transmitted for intensity (1.5 bits) and quality (4.0 bits) would combine for a total of 5.5 bits or 48 categories. These results were analyzed according to a multivariate procedure (8).

The results are presented in Table 4 which shows that 3.51 bits were transmitted for quality and .27 bits for intensity. Taking into account the small interaction of .09 bits for the interaction between quality and intensity, it is indicated that 3.60 bits were transmitted about quality for a specified intensity and .36 bits about intensity for a specified quality. Again it is clear that intensity did not add much to the distinctiveness of the odor stimuli, although the first experiments indicated that the observer is capable of identifying at least categories on this dimension.

Table 4

Means and SDs of bits of information transmitted by five Ss for 3 levels of intensity for 16 odorants

Transmission	Mean	SD
Quality—Responses	3.51	.14
Intensity—Responses	.27	.05
Interaction	.09	.01

The last experiment investigated maximum channel capacity for odor quality. Five, 7, 10, 15, 24, and 36 odor stimuli in 100% concentration were presented consecutively to each observer. Both similar and different odor stimuli were used. The results in Figure 4 show that performance improves up to 24 categories but that no further improvement results from presenting a larger number, while efficiency is greatly reduced. Again the difference between so-called similar and different odor stimuli is verified.

Conclusion

The present findings, then, indicate that an average relatively-unpracticed observer can learn to identify correctly three levels of intensity. The results also show that a well-practiced observer can identify four or five levels of intensity. There is a small but reliable improvement in the accuracy of intensity judgments with increase in the concentration values of the stimuli and in the size of the step between the stimuli presented for judgments. Increasing the number of alternative stimuli judged did not influence these results appreciably and no departures were obtained from these intensity results with four different odorants.

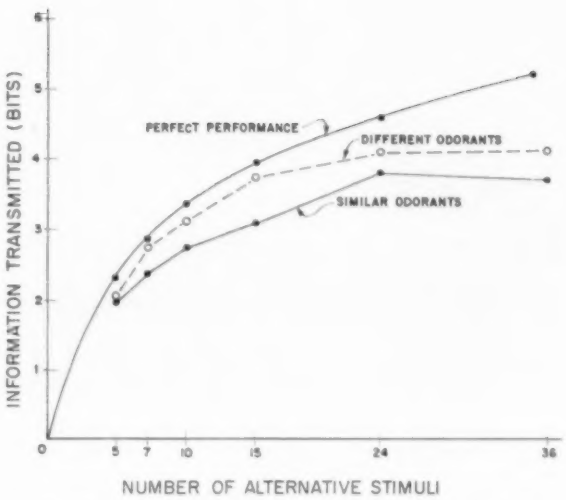

Fig. 4. Amount of information transmitted by five observers about odor quality as a function of number of alternative stimuli for two kinds of odor.

The experiments on odor quality indicate that these observers could identify about 16 different odor qualities without error. These results were influenced by variations in the sample of odor qualities but not appreciably by the intensity characteristics.

The accuracy of judgment when both intensity and quality were varied in the odors presented to the observer did not exceed that obtained for quality alone. Thus as information was added to the sensory display, the accuracy for intensity was drastically reduced.

Thus, the results show that the human observer has a much greater capacity for discriminating and remembering odor qualities than odor intensities. In general, all the indications of the present experiments are that judgment of odor by sniffing shows the same characteristics as do judgments in other sense modalities.

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PHYSIOLOGY of OLFACTION

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MAN POSSESSES SEVERAL odor detecting systems from which he may receive information concerning the chemical environment in which he is living. The olfactory system, with its millions of individual odor-detecting receptors, has long been studied in man. However, the nasal trigeminal nervous system and the Jacobson's or vomeronasal organ of lower forms of mammals have been little studied and therefore little understood.

Most of our information concerning olfaction has been obtained from the measurement of threshold concentrations of odors and the study of olfactory adaptation or fatigue. In many cases, however, such information tells us little about the sense organ and therefore little of the mechanism by which the odor stimulates the olfactory receptor.

The living animal continuously receives information about its environment through its senses. This information is always transmitted from the sensory organs to the central nervous system in the form of nerve impulses and the associated electrical events can be detected with suitable amplifiers and recording equipment. Thus the sensory nerves may be tapped in on, and the messages going to the brain from the sense organs can be revealed. Considerable success has been attained in the study of the various senses with this method. It is important to understand that the technique is designed to study the functioning of the sensory organs. The essentially unsolved problem of how nerve impulses are generated and propagated is not attacked directly.

The response of the olfactory receptor to various odors may be recorded directly by electrically measuring the neural response, for the nerve fiber is an integral part of the olfactory sense cell. The electrical and physiological approach to the study of olfaction allows one to determine the relationship between the stimulus and the response, the latter in terms of nerve impulses per unit time. Thus, objective and quantitative information can be obtained concerning the response of the receptors, information which is not easily obtained in any other manner.

When the electrical neural activity is recorded from a very small bundle of the primary olfactory nerves in an anesthetized animal, it is found to increase in

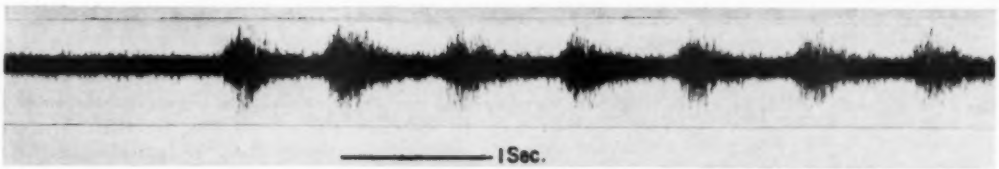

Fig. 1. A recording of the electrical neural activity of a very small bundle of the primary olfactory nerves in an anesthetized animal. The activity increases in magnitude during inspiration of an odor and decreases at expiration.

magnitude during every inspiration of an odor and to decrease during expiration, Fig. 1. The maximum height of this activity gradually declines at high odor concentrations because of adaptation of the receptors to the odorous stimulus. At low and medium odor concentrations, however, the magnitude of the activity during successive inspirations is constant. It is believed that the adaptive behavior of the sense of smell to low and medium odor concentrations is not due to sense organ adaptation, but is attributive to an adaptive process in the olfactory bulb. The olfactory bulb is the first center in the brain to which the olfactory information is transmitted.

In order to gain a better understanding of the mechanisms involved in olfaction, one needs to measure the response accurately. A quantitative measure of the response from a small population of olfactory receptors may be obtained by electronically summating the neural signals in a small twig of the nerve, Fig. 2. Since the response depends markedly upon the concentration of the odor, it is necessary to obtain a relatively pure odor of known concentration in performing quantitative experiments upon the olfactory system. This may be achieved by passing room air through silica gel and activated charcoal, to clean it, and by saturating this air with the vapor of the odorous stimulus.

The odor saturated air may then be diluted in a known manner, using flow meters, and the concentration varied. Odor is presented to the animal by flowing the diluted, odorous air stream through a breathing chamber into the side of which the animal's nose enters. Using a sufficiently high flow rate ensures that the desired concentration of odor reach-

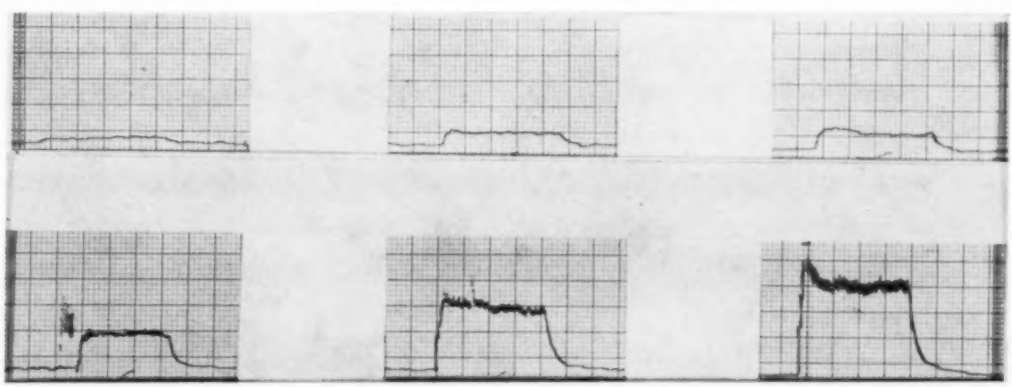

Fig. 2. The response must be measured accurately. A quantitative measure of the response from a small population of olfactory receptors can be obtained by electronically summating the neural signals in a small twig of the nerve.

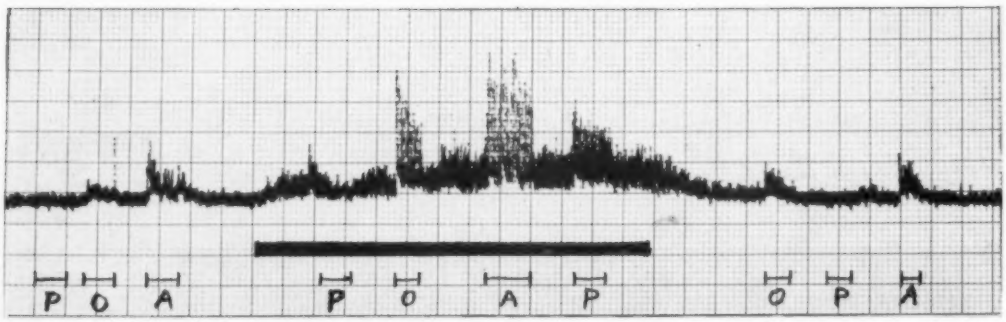

Fig. 3. In the rabbit, stimulation of the sympathetic nerve increases the olfactory response to a given odorous stimulus.

es the nares (nostrils) each time the animal inhales.

Since the individual olfactory nerve fiber is a part of the receptor cell, it is called the primary olfactory nerve fiber. A measurement of the olfactory neural activity is, therefore, a more direct indication of the response of the receptor than can be obtained from similar recordings in the olfactory bulb. It is also more indicative of the type of information being transmitted from the sense organ to the brain than are the electro-olfactograms recorded by Ottoson (6) and by Takagi and Shibuya (9).

Olfactory accessibility

In many animals, the olfactory receptors are not in direct communication with the air stream as it goes through the nasal passages. The receptors in the rabbit can be found on the nasal septum and turbinates. One of the passages can be considered as being bounded by two parallel plates, one plate being the septum, the other the turbinate, separated by a distance of about one millimeter. This distance increases upon stimulation of the sympathetic nervous system, because the blood vessels constrict, and thus allows more odor to pass by the olfactory receptors. In the rabbit, then, stimulation of the sympathetic nerve increases the olfactory response to a given odorous stimulus, Fig. 3.

In turn, the amount of sympathetic neural activity coming to the nose depends on the environment of the animal. For example, even though the animal is under anesthesia, if one pinches the toe, shines a light in the eye or claps one's hands, sympathetic activity increases the blood vessel constriction in the nose and the magnitude of the olfactory response increases. Such is probably the case in man also.

However, in certain animals, such as the tortoise, the olfactory mucosa lines a blind cavity that communicates with the respiratory passageway. The connecting aperture can be seen to decrease markedly in size when the sympathetic nerve is stimulated. Thus, there is a dramatic reduction of the olfactory response to an odor in the tortoise when the sympathetic nerve is stimulated. On the other hand, additional experiments with the tortoise show that the olfactory accessibility can be increased relative to its resting state.

The demonstration of such dependencies of the olfactory response upon the condition of the autonomic nervous system is significant, for the general state of excitability of man may play a great role in the variations of human response to odors in one individual at different times and between individuals. It is well known that variation in nasal patency of the human affects ability to smell. The influence that the degree of olfactory accessibility has upon the olfactory response is to be seen in experiments in which both the odor concentration and the nasal flow rate are varied.

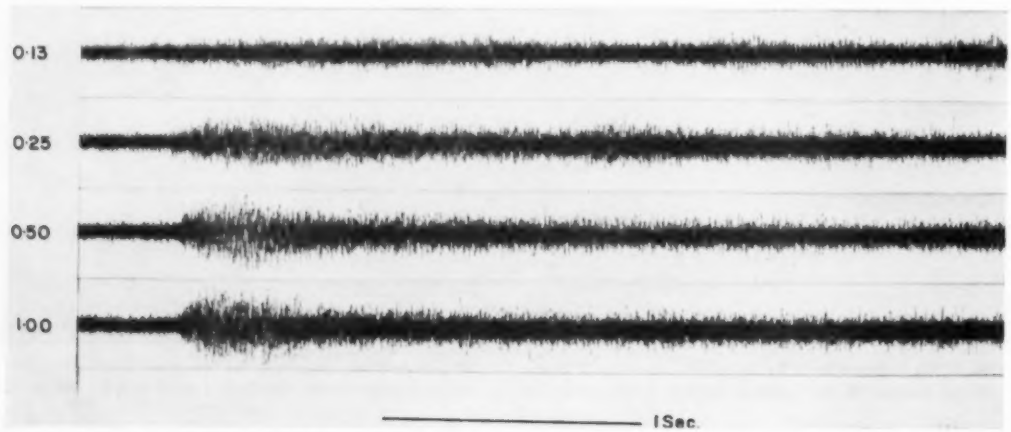

Fig. 4. Initially there is an increase of electrical activity in the olfactory nerve when a given concentration of odor is flowed through the nares at a constant rate. Response may increase with flow rate until "saturation" is reached.

It has already been shown that the magnitude of olfactory response depends on the accessibility of the odor to the olfactory mucosa. It would be assumed from such experiments that the rate of flow of the odor over the olfactory area is an important parameter in the olfactory response. Such can be shown to be the case.

Fig. 4 shows that there is initially an increase of electrical activity in the olfactory nerve when a given concentration of odor is flowed through the nares at a constant rate. This is done with a syringe attached to a cannula in the trachea. The initial response may increase with flow rate until a high enough rate is obtained that no further increase in response will be obtained as the flow rate is increased.

Flow rate is almost as important a parameter as the concentration of the odor, as shown in Fig. 5, where the response magnitude of the receptors of the tortoise is measured at different concentrations and different flow rates. At high flow rates the residual contaminating odors in the air stream may become important. The elimination of contaminating odors is a difficult problem. It can be shown with careful studies that an increase in response at high flow rates to so-called purified air is not due to a mechanical factor in stimulation but rather is due to residual odors.

Trigeminal nerve activity

The olfactory receptors are not the only neural elements in the nose that may respond to odor. In man, for example, the terminations of the trigeminal nerve which innervate the interior of the nose also respond to odors. It is experimentally possible to record from the trigeminal nerve simultaneously with the olfactory nerve and to compare the magnitudes of responses in these two receptor systems at different odor concentrations. When this is done, it is found that with many odors the olfactory receptors are more sensitive than the trigeminal nerve endings. That is, at low odor concentrations the olfactory receptors may respond, but the trigeminal nerve not.

The trigeminal nerve may respond after a rather long latency of a few seconds at high odor concentration and a response increases with time. The trigeminal nerve endings fully respond by the time the olfactory receptors have completely adapted to the odor stimulation at high concentration. It is not true, however, that only irritating odors stimulate the trigeminal nerve endings. For example, in the rabbit, the odor of phenyl ethyl alcohol may stimulate the trigeminal nerve endings at a lower concentration than that for the olfactory receptors. The odor of phenyl ethyl alcohol is rather mild and flower-like and was often thought to be a pure olfactory odor. From such experiments we have concluded that it is difficult to tell before experimental evidence is available which odor will stimulate the olfactory receptors at lower concentrations than the trigeminal threshold concentration.

The importance of the trigeminal nervous system to the animal is not too well understood. It may not have a large role in sensation, although it does control a number of reflexes which indirectly affect the magnitude of the olfactory response. The trigeminal nerve may also play a larger role in the detection of odors by animal forms other than man.

Vomeronasal organ

Most animals have an accessory olfactory organ in the front part of the nose, the vomeronasal or Jacobson's organ. This organ is vestigial in man and therefore need not be considered in human sensation. Since the receptors in this organ look similar to olfactory receptors, it has long been thought that they might respond to odor. However, a direct experimentation by Adrian (1) indicates that this may not be the case. Our laboratory studied this problem, using a tortoise, and recorded responses from the vomeronasal organ simultaneously with those from the ol-

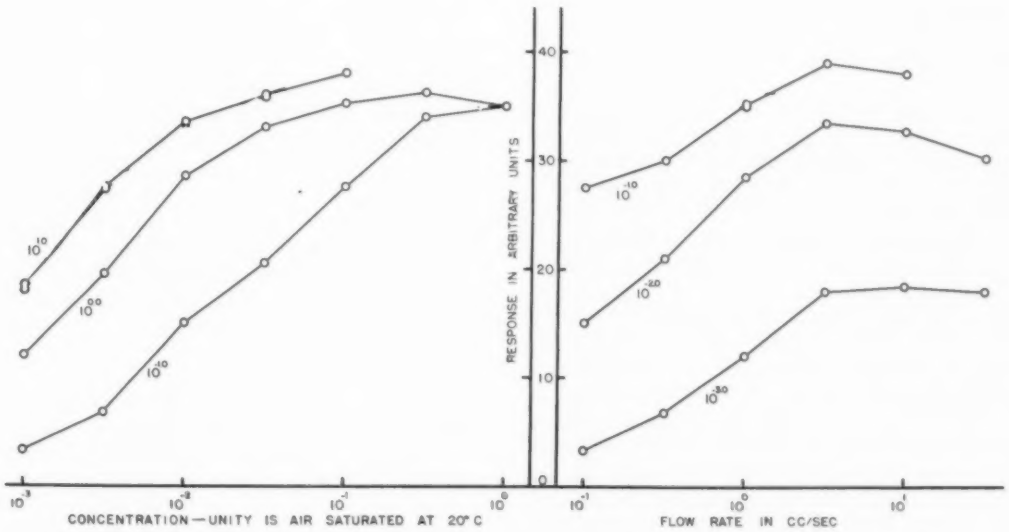

Fig. 5. Flow rate is almost as important a parameter as the concentration of the odor. The response magnitude of the receptors of the tortoise was measured at different concentrations and different flow rates.

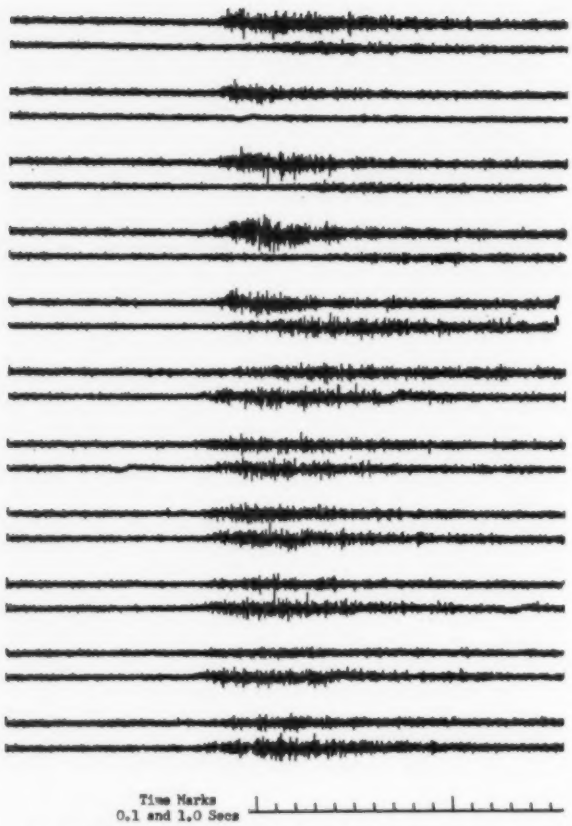

Fig. 6. Simultaneous recordings from small twigs of the vomeronasal and olfactory nerves are shown.

factory receptors. It was found that the vomeronasal organ responds very well to odorous stimulation.

Simultaneous recordings from small twigs of the vomeronasal and olfactory nerves are shown in Fig. 6. The stimuli are fatty acids: formic, acetic, propionic, butyric, **n**-valeric, **iso**-valeric, hexanoic, heptanoic, octanoic, nonanoic and decanoic acid. The vomeronasal response predominates for the lower members of the series, but there is a cross-over to olfactory predominance in going from **n**-valeric to **iso**-valeric acid.

The stimuli are controlled only in the sense that the strength of the puff is adjusted for moderate responses. Benzyl amine yields large responses in both kinds of nerve, but amyl pyridine apparently stimulates only the olfactory receptors. The acetate esters of the smaller aliphatic alcohols are very effective as olfactory stimuli, but afford very small vomeronasal responses.

Of the aliphatic alcohols, it is typical that only methanol and ethanol are good vomeronasal stimuli. However, an exceptional preparation was encountered in which the vomeronasal response peaked at butanol. This preparation was unusually responsive to straight-chain butyl and amyl alcohols, though quite insensitive to their **iso** isomers. Some of the results suggest that water solubility may be an important property of the odorant compounds that stimulate the vomeronasal receptors.

The ability to excite the olfactory receptors with an aqueous solution has long been disputed. For example, experiments by Proetz (7) indicate that the olfactory receptors of man do not respond to an aqueous solution of an odor. In those experiments where response has been obtained, one can always question whether or not a trapping of gas is not affording the stimulation in the nose. On the other hand, many theories, particularly the recent one by Davies and Taylor (4), suggest that the odorous molecules go from the vapor phase to the aqueous solution of the mucus and thence to the long olfactory cilia to which they are adsorbed. Thus, it should be possible to stimulate with an odor in an aqueous medium, just as occurs naturally in fish.

In such experiments with air breathing animals, it is important to obtain an aqueous medium of the right ionic and osmotic contents, such that the solvent itself does not stimulate or inhibit the receptors. By careful analysis and further electrophysiological experimentation, a satisfactory medium was found, one in which an odor could be dissolved. The aqueous solution itself must be free of contaminating odors. It is important to use double distilled water and to pass it through a column of activated charcoal to remove residual odors. The olfactory response obtained with aqueous solutions of odors displayed the same features that were observed with the use of the air olfactometer, Fig. 7.

Interpretation of olfactory data

It is clearly seen from the recordings presented that it is difficult to obtain a good steady-state olfactory response. However, the transient part of the response occurring at the beginning of the odor presentation is rather well behaved. The physiological mode, of course, is intermittent stimulation, occurring with each inspiration of air. The averaged on-responses to amyl acetate are plotted in Fig. 5 for an olfactory preparation. The same data are plotted two ways: response as a function of concentration; and response as a function of the nasal flow rate.

It is apparent that the response approaches some upper limiting value with concentration of amyl acetate. At the highest concentrations the adaptation mechanism appears to take over before the stimulation mechanism has exerted its full effect. Also, the trigeminal effects at these concentrations should be recalled. The olfactory response is as dependent upon

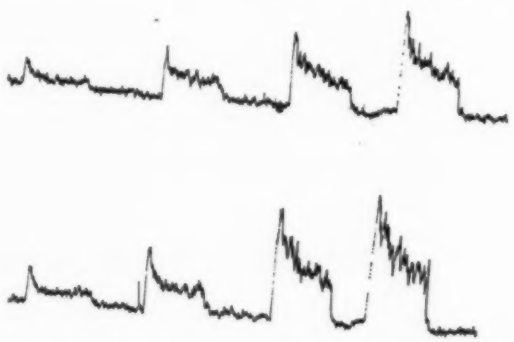

Fig. 7. The olfactory response obtained with aqueous solutions of odors showed the same features that were observed with the use of the air olfactometer.

the nasal flow rate as it is upon the concentration in the lower portions of their ranges. Moreover, for the lower concentrations, the response as a function of flow rate tends toward some limiting value that is characteristic for the particular concentration.

The dependence of the olfactory response upon nasal flow rate has been predicted by Stuiver (8). The prediction resulted from a consideration of the effects of adsorption, absorption and diffusion of the odorous molecules in the nasal passages. Without going into the quantitative aspects of Stuiver's theory, it is important to note that it predicts both features of the response dependence upon flow rate. Namely, the increase with flow at low rates and the approaches to limiting values at high rates. Experiments of the type described here show that the quantitative dependence of the olfactory response upon flow rate varies markedly for different odors.

Although for benzyl amine the response did not reach a limiting value in the range of flow rates available, it can be inferred that it would, if the nasal flow rate could be sufficiently increased. There is an obvious correlation with water solubility. Benzyl amine is miscible with water in all proportions, but amyl acetate saturates at about 14 millimolar. The solubility of amyl acetate is even less in salt solutions, and the mucous environment of the olfactory receptors is of this nature.

Consider a slightly soluble compound, such as amyl acetate, and the vastly smaller rate of diffusion in water as compared to air. It can be argued that the surface concentration approaches equilibrium with the air concentration at sufficiently high flow rates, corresponding to the limiting values observed for the olfactory response. If the assumption is made that the receptor sites are situated on the terminal portions of the olfactory sense cells, near the mucus-air interface, one then knows the activity of amyl acetate at the receptors for certain of the responses: namely, for the limiting values obtained at high flow rates. It is unfortunate that the concentrations available from the olfactometer do not go lower than one part per thousand.

In general, of course, the values for concentrations from the olfactometer are valid only at the naris. However, the additional assumption can be made that the curves of response *vs.* concentration are related by constants. That is, for a certain lower flow rate, the concentrations at the receptors are a particular fractional value of the known concentrations at the naris.

This assumption then allows us to translate the lower curves in the left hand part of Fig. 5 to determine whether the overlapping portions will coincide. The results of such an operation can be described by a smooth curve drawn through the points. The curve is of an equation describing the binding of amyl acetate molecules by two kinds of receptor sites. The curves for the two types of receptor sites separately are of the form:

$$R = R_{max}\frac{KC}{1 + KC}$$

where R is the response, C the concentration and K the equilibrium constant.

The equation is the same one that Beidler (3) has successfully applied in describing taste data. Interestingly enough, it is only successful in describing the transient olfactory response. The steady-state response appears to involve a labile adaptation mechanism. In fact, some features of the olfactory response bring to mind Mullins' (5) narcosis theory of stimulation. Also, Mullins found evidence for two kinds of olfactory receptors.

Conclusion

Odors inhaled through the nose may be detected by receptors associated with fibers contained in the olfactory, vomeronasal and trigeminal nerves. This applies to the common laboratory animals, although the vomeronasal organ is vestigial in the human. Hence it becomes clear that attention should not be directed exclusively toward the olfactory receptors in experiments involving subjective or behavioral responses.

Quantitative measurements of the olfactory response can be made with electrophysiological methods. The attractive possibility of going beyond the usual threshold studies is thus presented. The experiments that have been described indicate how this can be done. Results show that a threshold determination gives an incomplete description of the interaction between an odor and the olfactory receptors. The maximal response and equilibrium constant are necessary for a complete description. Physical chemical studies of the adsorption of odors to various kinds of surfaces may give useful information about the physical properties of the molecules, but no direct information concerning the binding of molecules by the olfactory receptors.

An adequate understanding of the sensation of smell in response to an odor is not obtained by keeping the attention focused at the receptor level. Adrian (2) has stressed the importance of the spatial and temporal patterning of the stimulus over the whole of the olfactory organ. The extreme flow rate dependence of the olfactory response is appropriately noted. The information introduced in this paper must be synthesized into a coherent picture to understand the events occurring in the nose during a single sniff.

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Odor and Molecular Constitution

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I FIND MYSELF in the unusual position of an organic chemist, addressing a meeting consisting of distinguished perfumers on a subject which is pure pharmacology. The fact that both the audience and the speaker are interested amateurs rather than professionals, encourages me to allow my imagination a trifle more elbow-room than I would have dared to do when discussing a subject belonging to organic chemistry.

What I am going to tell you has little to do with science. On the contrary, it is a personal opinion, based upon what I have learned by looking my molecules in the face, by trying to understand their mentality and to predict what they will do when permitted to enter my and other people's noses.

Although it is an unproved and for the moment, unprovable opinion, I believe that, in broad lines, it represents the truth or rather part of the truth, since it has served me well in the course of my work and continues to do so. You will understand that my position in industry prevents me from describing most of the molecules I have met in the course of my work, but I shall mention a few examples which I hope will illustrate my point of view and interest you at the same time.

Introduction

In the following discussion we shall assume the existence, in the internal part of the nose, of receptors, i.e. of tissues of specific structure, the interaction of which with molecules of the odorant causes the stimulus, and we shall follow the general practice in modern pharmacology to treat the receptor entirely as a hypothetical structure, which gives rise to the biological response when the interaction takes place, without making unjustified assumptions about their properties and structure.

A second assumption we make is that material contact between the molecules of the odorant and the receptor organ of the nose is required for the interaction. This means in the first place that a compound must have sufficient volatility to render such a contact possible and in the second place that we discontinue considering the so-called radiation theories seriously, which seems to be fully justified after the arguments given by Thompson (1) and by myself (2).

The process of olfaction may be divided roughly into the following stages:

1. A current of air, carrying molecules of the odorant, enters the nose and the molecules approach the surface of the receptor organ up to interaction distance.

2.1 Interaction between stimulant and receptor organ takes place.

2.2 As a result of the interaction the stimulus is formed.

2.3 The molecules of the stimulant or their degradation or conversion products are removed from the interaction zone.

3. The stimulus is transferred to the olfactory part of the brain and translated into an odor sensation.

We shall concentrate our attention entirely on one of these steps, i.e. the interaction between the stimulant and the receptor organ.

In a recent paper (2) I have given an extensive critical discussion of all existing theories on the mechanism of this interaction, I have tried to separate the chaff from the wheat and to find a common denominator of the most valuable theories. This common denominator was found clearly to be the external shape of the molecule as the decisive factor in olfaction and from this and from other considerations I derived a tentative and far from complete model

of the mechanism of the interaction step which I called the "profile-functional group" or "P.F.G." concept.

My main object is to develop this concept a little further and to see in how far it is corroborated by our present knowledge in this field.

Profile-functional group concept

The interaction of a molecule with the receptor organ is characterized by the affinity of the molecule to the receptor surface and by its efficacy, i.e. the ability of the molecule, when absorbed, to set off the stimulus.

So far we are closely following Stephenson's (3) concepts which have generally been accepted in pharmacology.

The first, the affinity, is mainly determined by the functional group or groups and the second, the efficacy, mainly by the outward shape, the profile of the molecule in the orientation in which it is attached to the receptor surface when the interaction takes place. Both the affinity and the efficacy contribute to the physiological activity.

The orientations of all molecules at the receptor surface are statistically distributed around one or some energetically favorable ones and form a pattern, the shape of which is entirely determined by the nature, position and steric environment of the functional group or groups in the molecule.

The functional group may become attached reversibly to some ionic site at the receptor surface while the rest of the molecule interacts physically with a second site in analogy with the mechanism of e.g. the interaction of acetylcholine with cholinesterase. A second possibility, analogous with the behavior of soap molecules at an oil-water interface, is that the molecules of the stimulant are arranged at an interface between two phases, in orientations for which the solvation or, more specifically, the hydration tendency of the functional group is responsible. However at this moment it is not necessary to settle this question.

The orientation pattern must be assumed to be represented by a Gauss curve which has a high narrow appearance (Fig. 1, A) when the affinity is high and this is the case when only one, easily accessible functional group is present and practically all molecules are found in one strongly favored orientation.

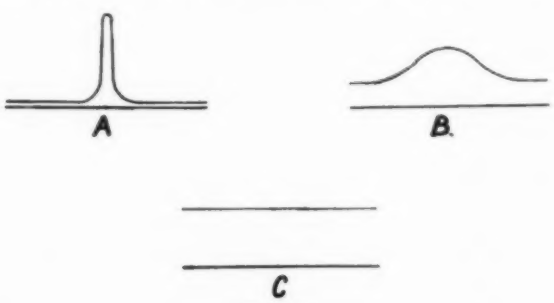


Figure 1

At lower affinities, i.e. when the molecule has more than one different functional groups or a sterically hindered functional group the population of the random orientations increases and the curve shows a wide, shallow form (B).

When finally, no functional group or a sterically inaccessible functional group is present, only random orientations can occur and in the extreme case the distribution curve becomes flat at zero affinity (C).

While the functional group determines the affinity of the molecule, its profile in combination with its orientation is responsible for the activity, i.e. in this case for the nature of the stimulus.

The mechanism of stimulus formation is unknown but it is attractive to assume that the profile in its actual orientation fits perfectly or imperfectly into a second site of the receptor surface and, in this position disturbs some unknown process or situation which normally takes place or exists at this surface without causing the formation of a stimulus. Several interesting theories on this process are waiting for experimental support. Anyhow, the interaction mechanism may be safely assumed to have vectorial aspects. Consequently, a number of identical molecules, absorbed in different orientations at active sites of the receptor surface, behave as if they had different profiles and each of them sets off a molecular stimulus with specific quality and strength. The total stimulus is formed by superposition of all molecular stimuli.

In cases where one easily accessible functional group is present, the orientational pattern is of type A, i.e. practically all molecules have the same, energetically favorable orientation. In Fig. 2 the orientations have been represented arbitrarily as arrangements in an interlayer but of course many other types of orientation are possible.

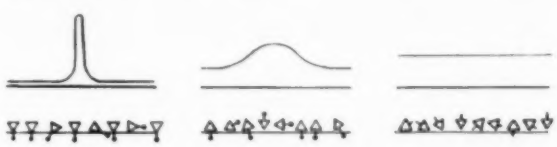


Figure 2

In case A the average profile which determines the total of superimposed stimuli is equal to that of each individual profile. Structural details are clearly discernible and structural changes have a clearcut influence upon the nature of the stimulus.

As the population of the random orientations increases (B) the difference between the average profile and the profile of the individual molecule becomes more important and the influence of structural details upon the stimulus becomes less specific. In case C with only random orientation the structural details are no longer discernible in the average profile and their influence upon the stimulus is completely blurred. This case is of course entirely hypothetical since even the orientations of saturated hydrocarbons at an interface, due to van der Waals forces are not all energetically equivalent and their frequency distribution may be assumed to show a shallow curve.

The intensity of the stimulus is dependent partly on the concentration of the odorant in the air and partly on the concentration of the molecules of the odorant in the interlayer of the receptor organ in biologically active orientations. Such orientations do

not necessarily coincide with the energetically preferred orientations.

A molecule in a preferred orientation may very well be biologically inactive whereas in a different, energetically less favorable orientation its profile may cause the formation of a stimulus. In the latter case however, the concentration of molecules in biologically active although energetically unfavorable orientations is too small to trigger a strong stimulus and the odor will be weak. In cases where many types of orientations are biologically active, also random orientations may lead to a strong stimulus but this is invariably characterized by lack of a definable character and by a weak influence of structural variations.

We shall now see in how far this outline is corroborated by the present stage of our knowledge in the fields of anatomy, physiology, pharmacology, and structural chemistry.

Anatomy

As you know, both nasal cavities are divided into the lower or respiratory region and the upper posterior part, the olfactory region, both of which are covered with a continuous mucous membrane.

In the respiratory region this membrane is covered with a ciliated epithelium with columnar cells, smaller pyramidal cells and a few mucous or goblet cells. The membrane in the olfactory region is thin and yellow and it contains the peripheral endings of the olfactory nerve. It is covered with nonciliated columnar epithelium, the cells of which may be divided into three different types (Fig. 3).

Three characteristic details of the olfactory membrane deserve our attention, its size, its pigmentation and the olfactory hairs.

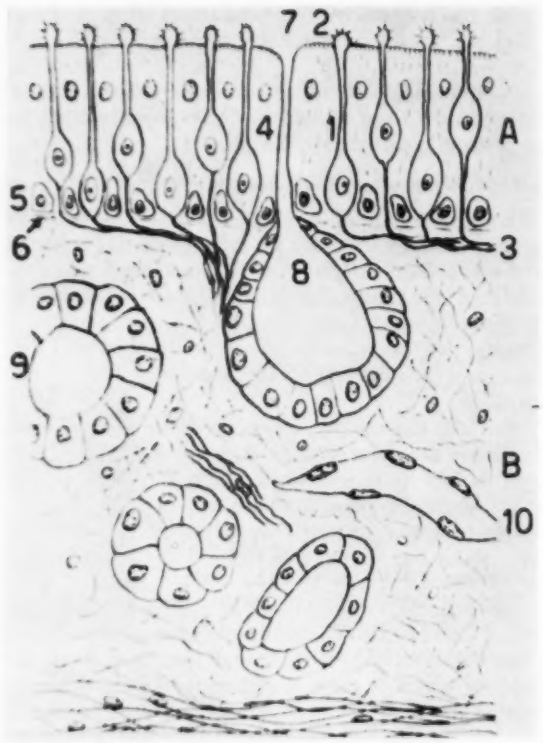
The surface area of the olfactory epithelium is 5 cm^2 in adult man, i.e. much larger than that of the retina. This is important for a satisfactory explanation of the phenomena of olfaction since discrimination is more favored by a clearly distinguishable signal than by a strong one and, as Adrian expresses this, it is obvious that a picture on a large canvas can show more detail.

The color of the olfactory membrane varies from light yellow in man to yellow-brown or yellow-red in macrosmatic animals.

Since Ottoson (4) demonstrated that olfactory stimulation is limited to the yellow region we have reason to believe that the pigments of this region play a part in the mechanism of the interaction. Little is known, however, about their nature or function. Milas (5) found that it contains considerable amounts of vitamin A and carotenoids.

Ottoson's (4) work also suggests that the olfactory hairs play an important part in the generation of the stimulus. He found that the amplitude of electrical responses decreases as the depth from which they are recorded increases. Consequently the response originates from structures close to the surface which may be identical with the olfactory hairs.

The conclusion is that the olfactory region shows a number of details which, although their function is still cryptic, can easily be imagined to be the tools for the surprising diversity of odor sensations we observe.



From M. A. Gerebtzoff, J. Physiologie **45** (1933) 251.

Figure 3

The cylindrical supporting cells (4) extend over the whole depth of the olfactory membrane. They have oval nuclei situated at the base of the columnar part of the cell. The basal cells (5) lie between the lower ends of the supporting and of the olfactory cells.

The olfactory cells (1,2) are bipolar nerve cells consisting of a cell body, a central and a peripheral extension. The cylindrical peripheral part, which extends between the columnar parts of the supporting cells, pierces the external membrane formed by the latter and ends in a spherical body, covered with 6-8 hair-like recesses known as the olfactory hairs, with dimensions of about 0.2 μ.

The small central part of the olfactory cells pierces the basal membrane (6) and joins the central extensions of other olfactory cells (3) forming a network under the basal membrane. They pass into the cranial cavity after which they enter the olfactory bulb, in the glomeruli of which they divide and form synapses with the dendrites of the mitral cells.

Physiology

The main contributions to our understanding of the olfactory system have been provided by the electrophysiological studies of Adrian, Ottoson and others. It is impossible to give in this paper a complete survey of this extensive field and I shall limit myself to some of the most significant results.

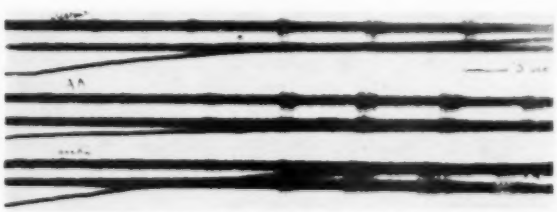
In most cases the electrical response following chemical or mechanical stimulation of the olfactory membrane was recorded by means of one or two

electrodes in the olfactory regions of the brain. Fish, rabbits, cats and frogs have been used for these experiments, while Sem-Jacobsen (6) had an opportunity to carry out a series of experiments on the human brain. Ottoson (4) studied responses from electrodes in the olfactory epithelium of the frog. The results of this work which are most important for our subject are that the distribution pattern of the sensitivity to stimulation over the surface of the olfactory membrane is different and characteristic for each stimulant and that this pattern corresponds with a similar pattern of response distribution in the olfactory bulb. I shall illustrate this by means of a few simple examples.

Le Gros Clark (7) found that the removal of varying parts of the olfactory bulb of the rabbit led to degeneration of specific regions in the olfactory epithelium and he concluded that there is a significant degree of regional projection of the olfactory epithelium on to the olfactory bulb. Consequently both have their own geography, both can be mapped and the corresponding regions in both maps can be located.

Adrian (8) studied the oscillograph recordings from an electrode in contact with the mitral cells in the olfactory bulb and found characteristic differences in the time distribution of the impulses for different odorants. Ethyl acetate gives an abrupt discharge which ends simultaneously with the air movement while the impulse caused by stimulation with pentane rises gradually and continues after the air movement has stopped.

Electrodes in the anterior part and in the posterior part of the bulb give different recordings which are specific for each stimulant. This is illustrated by Fig. 4 which shows recordings by stimulation with acetone, amyl acetate and a mixture of alkanes. In all

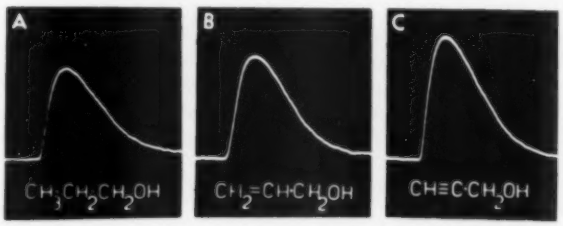


From E. D. Adrian, Acta Physiol. Scand. **29** (1953) 10.

Figure 4

three sections the upper recording is taken from an electrode in the oral region and the lower from one in the aboral region of the olfactory bulb. The signal line shows increasing concentration of the stimulant. Acetone causes only discharges in the oral region, alkanes in the aboral region and amylacetate in both. A certain geographical differentiation in the olfactory bulb and consequently also in the olfactory membrane according to lipoid- and water solubility, is suggested by these results. Also the types of impulses of these three odorants differ considerably. That of acetone consists only of large spikes, of pentane of low spikes, while the impulse caused by amyl acetate consists of both types.

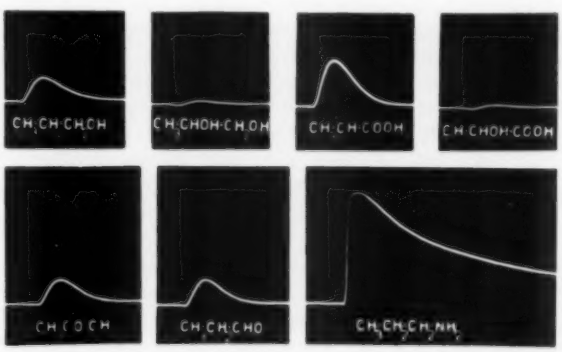
The effect of molecular structure upon the stimulatory efficiency is perhaps demonstrated best by the work of Ottoson (9) who studied the recordings taken from electrodes in the olfactory epithelium of the frog. These recordings consist of a slow potential change which is characteristic for the stimulatory efficiency of the odorant.



From D. Ottoson, Acta Physiol. Scand. **43** (1958) 169.

Figure 5

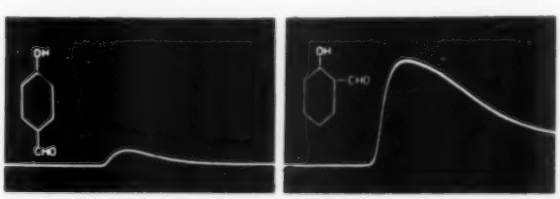
Fig. 5 shows the increase of the stimulating power in the series propyl alcohol, allyl alcohol and propargyl alcohol.

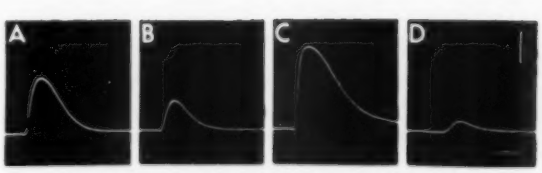


From D. Ottoson, Acta Physiol. Scand. **43** (1958) 169.

Figure 6

The upper series of Fig. 6 illustrates the effect of the introduction of a second functional group, in this case a hydroxyl group into propyl alcohol and propionic acid. In both cases the stimulus is practically completely destroyed. These experiments were carried out by blowing about 0.5-1 ml of odorous air,





From D. Ottoson, Acta Physiol. Scand. **43** (1958) 170.

Figure 7

obtained from aqueous solutions of equivalent concentrations on to the nasal mucosa. According to this technique however, the concentrations of the glycol and the hydroxy acid in the air are certainly lower than those of the parent compounds and at least part of the drop in stimulating effectiveness should be explained by the decreased concentration.

In the lower series the stimuli of acetone, propionic aldehyde and propylamine are shown. Since the volatilities of these compounds are very close, no important concentration effects can play a part and the extreme efficiency of the amino group is clearly demonstrated.

Fig. 7 demonstrates that the presence of two efficient functional groups in remote positions decreases the effectiveness which could very well be explained by an increased influence of random orientations since the same functional groups in vicinal positions cooperate and act as one single functional group, which favors one specific orientation and increases the stimulating efficiency.

However, chelation and consequently also in this case increased volatility of salicylic aldehyde introduces a concentration effect which tends to blur the overall picture. This complication is absent in the lower series of this figure in which the potential changes for n-butanol (A), isobutanol (B), sec. butanol (C) and tert. butanol (D) are shown. Evidently screening of the functional group (D) increases the influence of random orientation and decreases the stimulating efficiency.

Sem-Jacobsen (6) studied the electrical responses in the olfactory bulb of human patients and found that the shape of the response is weakly characteristic for each odorant. Stimulation of the nasal mucosa caused a rhythmic potential change superimposed over the resting or background activity with frequencies which varied between odorants. The frequency of the response for coffee was 30-34 cps, for lavender 32-36 cps. Other stimulants caused wider frequency ranges such as 28-39 cps for onion and 25-35 cps for burnt rubber.

In at least one case (lilac) the recorded frequency showed a periodic waxing and waning which seemed to be the result of more than one superimposed term and this suggests that the interaction of the odorant with the receptor organ causes an electrical response in the olfactory bulb with a spectrum of frequencies rather than a single frequency. Unfortunately the author selected practically only very complex odorants instead of pure chemical compounds. It is striking how frequently the physiologists could have increased the value of their often brilliant work by seeking the advice of their colleagues in the field of physics and chemistry. More than anything else the problem of olfaction asks for cooperation.

Adrian's work indicates that in olfactory discrimination spatial factors, created by different or even specific sensitivities of the receptors as well as temporal factors, determined by the time course of excitation play the main part and the suggestion lies close at hand that a given odor is recognized by the spatial and temporal pattern of the olfactory excitation it brings about. This is corroborated by the results obtained by others. Adrian interpreted the temporal aspect by means of the different rates of diffusion into the nasal cavities and by the folding of the mucosa. Ottoson (4) however studied the time course of the response obtained by stimulation of the flat receptor sheet of the frog and found that the shape was nearly identical with that of the curve obtained by Adrian. This means that morphological details of the olfactory organ cannot be important and Ottoson suggested that the water- and lipoid solubilities of the stimulant may be the source of the temporal differentiation observed in the olfactory bulb.

After this short and incomplete survey we may draw the conclusion that part of the results of the electro-physiological work corroborates the P.F.G.-concept and that none of these results disagrees with it.

Pharmacology

Modern pharmacology has studied many types of interactions between alien molecules and the organism. It may be safely assumed that some important elements which most of these types have in common may be extrapolated to the type of which we know least, i.e. olfaction.

That the stereochemical aspect is one of the most striking examples of these elements is shown clearly by the extensive work on the activity of acetylcholine and its many structural variants which has been reviewed recently by Barlow (10).

In the pharmacology of acetylcholine, two specific sites of the receptor, the anionic site and the esteratic site are assumed to interact with the quaternary ammonium group which determines largely the efficacy and with the ester group which is mainly responsible for the affinity.

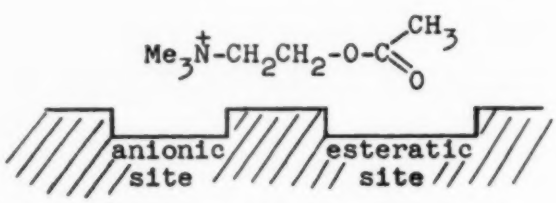


Figure 8

By varying one or both structural details the affinity and the efficacy can be influenced. Reduction of the molecule to tetramethylammonium destroys mainly the affinity, but the efficacy is, although considerably decreased, still present. The replacement of methyl in the quaternary ammonium by ethyl decreases the accessibility of the anionic site to a level which renders the normal interaction impossible. In this case the affinity is still sufficient but the efficacy is low and the ethylated compound acts as a competitive antagonist of acetylcholine, i.e. a compound of

similar structure which renders normal interaction impossible by blocking the receptor sites.

Competitive antagonists of acetylcholine can also be obtained by varying the "ester" part of the molecule. The many structural variations of the two groups of acetylcholine which have been studied indicate clearly that stereochemical aspects, such as absolute configuration and the steric requirements of the groups attached to the nitrogen and oxygen atoms, are extremely important for the activity of the compound.

I have mentioned this example only to show that the profile-functional group concept agrees well with modern trends in pharmacology.

Structural chemistry

In the present stage of our knowledge the most rewarding way to add to our insight in the relationship between structure and odor is to study classes of organic compounds with related odors and to see whether their structures have certain features in common which could be correlated with the odor.

By doing so, we accept two serious risks. In the first place we know that even the smallest traces of impurities with strong odors can alter the odor picture completely. It is far from impossible that traces of unknown impurities in aromatic chemicals play a more important part in perfumery than we are aware of but as long as they are present in reproducible quantities, this is not too important for practical work. However, in the study of olfaction the presence of trace impurities will lead to completely erroneous conclusions and this requires the utmost caution in the use and interpretation of older observations.

In the second place we should keep in mind that the observation that two different compounds have closely related odors can only mean that the odor impressions are similar. This does not necessarily mean that the fine structures of the stimuli leading to the formation of these impressions are also similar. They may be as completely unrelated as monochromatic orange and an orange color obtained by superposition of various other parts of the spectrum which may be indistinguishable to the eye. One musk odor may, for instance, be caused by interaction of the molecules of a compound A with receptors of a single type A, whereas a second musk odor can be the result of interactions of a molecule B in various orientations with a range of receptors of types B_1, C_1, D_1, etc., the superimposed stimuli of which are translated in the brain into the same musk impression. That this is not imaginary is suggested by Guillot's (11) observation on anosmia towards macrocyclic and steroid musks which he demonstrated to be completely independent.

However, if we wish to obtain information by comparing structures, we have to accept this risk which is at least partly neutralized by our being aware of it.

The P.F.G. concept enables us to formulate a number of predictions regarding the relationship between structure and odor which can be compared with our actual experience. The following are a few examples of such predictions.

1. The profile of a molecule with an easily accessible functional group is responsible for the odor type. The nature of the functional group is relatively unimportant as long as it guarantees a sufficient affinity.

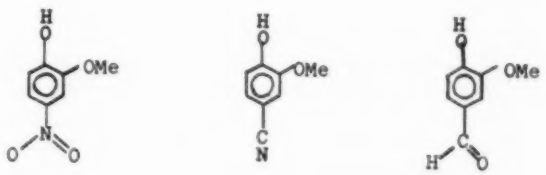
The classical example is the monosubstituted phenyl group which seems to be characteristic for the odor of bitter almonds.

I II III

Figure 9

Benzaldehyde, cyanobenzene and nitrobenzene are representatives of this odor type.

In the same way the 4-hydroxy-3-methoxyphenyl group possesses the profile which is responsible for the vanillin odor.



IV V VI

Figure 10

4-Nitroguaiacol (IV) and 4-cyanoguaiacol (V) have weak odors of the same type as vanillin (VI) (12). 3,4-Methylene-dioxyphenyl is connected with the heliotropin odor.

VII VIII

Figure 11

The aldehyde group in heliotropin (VIII) can be replaced by an azido group (VII) without changing the quality of the odor (13).

For the amber odor a combination of two fused six membered rings with a gem. dimethyl group (IX) seems to be a favorable profile group. This is dem-

onstrated by the structures of known amber compounds (X-XIII).

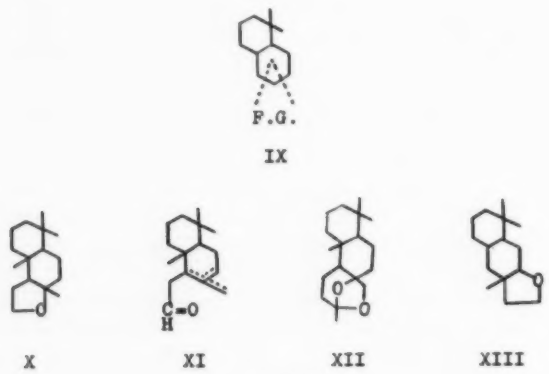


Figure 12

2. The odor type remains virtually the same when typical profile groups are replaced by others having approximately the same steric requirements and shape. Replacement of profile groups by groups with different steric requirements weakens or destroys the odor.

I have shown already that the functional group in heliotropin can be replaced by an azido group without changing the odor type.

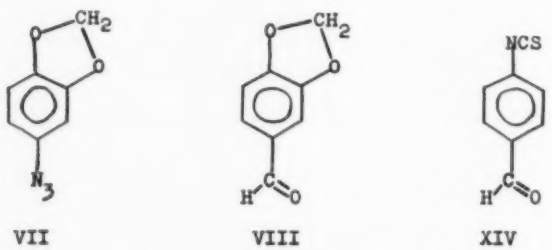


Figure 13

Replacement of the methylenedioxy group in heliotropin by a different profile group with steric requirements which screen the 3- and 4-positions, i.e. the isothiocyanate group (XIV) leads to the same result.

The largest group of compounds possessing a uniform odor type are the musks. At this moment six different structural classes of compounds possessing a musk odor are known in the literature, the macrocyclics, the steroids, the nitromusks, the indane musks, the tetralin musks and the benzene musks. This is certainly not the end.

It seems *a priori* improbable that compounds with such vastly different structures can have sufficient common morphological details to lead to the formation of similar odor impressions but my recent critical review of this field has shown that the combination of a sterically accessible functional group and a closely packed profile in a structure with a molecular weight of roughly 220-280 are criteria which probably suffice to obtain a musk odor. Since these criteria allow extremely wide structural limits, I expect that many more classes of musk compounds are waiting to be discovered. Up to now this prognosis has been fully corroborated by our experience.

Replacement of one of the methyl groups in musk xylene (XV) by bromine (XVI) leaves the musk odor intact (14).

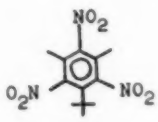
Figure 14

In the molecule of musk ambrette a replacement of the methyl group of the methoxy function by higher alkyl groups weakens the odor until, according to Carpenter (14), the butoxy compound is odorless.

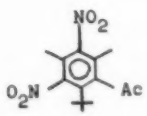
The methoxy group however, which is forced out of the plane of the benzene nucleus by the vicinal tert.butyl- and nitro groups, is an extremely important detail of the molecular profile.

Figure 15

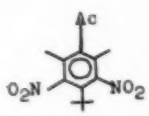
We could demonstrate this by the synthesis of XVIII, the structure of which is very similar to that of musk ambrette XVII and which was found to be odorless. Undoubtedly this is due to the fact that the profiles of both compounds are rather different. This is clearly visible in the models. In these examples pure profile groups are replaced. However, in the following cases it is less simple to find out whether we are tampering with the profile or with the functional groups.



XIX



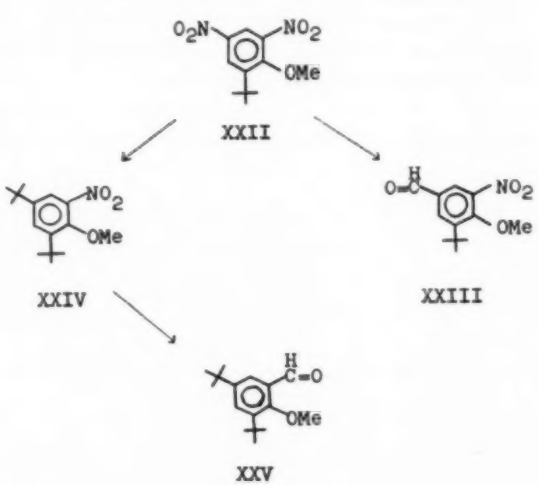
XX



XXI

Figure 16

Both types of nitro groups in musk xylene (XIX) can be replaced by acetyl groups (XX; XXI) without destroying the musk odor.



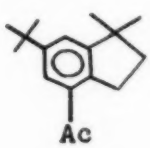
XXV

Figure 17

The sterically unhindered nitro group in XXII can be replaced by a formyl group (XXIII) as well as by a tert.butyl group (XXIV). Replacement of the remaining nitro group by formyl however results in a complete loss of the musk odor (XXV).

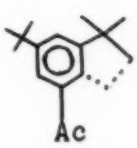
The best way to explain the large number of nitromusks seems to be to assume that nitro groups are bifunctional and can act both as functional and as profile groups. Also, an unusual number of different orientations must be able to contribute to the musk odor.

The picture presented by the aromatic nitrogen free musks is much simpler. Good examples are 4-acetyl-1, 1-dimethyl-6-tert. butyl-indan (XXVI) and 6-acetyl-1, 1-dimethyl-4-tert. butyl-indan (XXVII) both of which are strong musks.

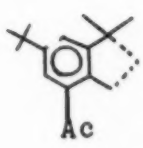


XXVI

XXVII



XXVIII

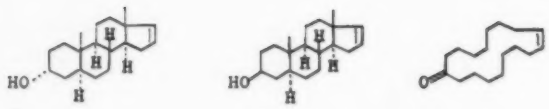


XXIX

Figure 18

This is quite comprehensible since their profiles possess quaternary carbon atoms in the 3- and 5-positions which are obviously responsible for the typical bulky musk profile. This suggests that the indan system is unessential for the musk odor and we could demonstrate this with the compounds 3,5-di.tert.butylacetophenone (XXVIII) which is still a rather strong musk and 2-methyl-3-isopropyl-5-tert. butylacetophenone (XXIX) which is a weak musk.

An interesting demonstration of the importance of the profile for the odor was found by Prelog and Ruzicka (15) who made the surprising discovery that 5-α androsten-16-ol-3 α (XXX) possesses a decidedly musklike smell.



XXX XXXI XXXII

Figure 19

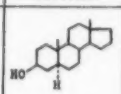
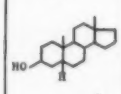
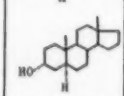
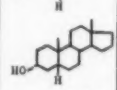
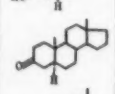
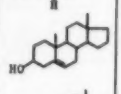
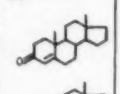
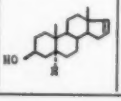
The odor of the corresponding 3 β-epimer (XXXI) was very much weaker. The authors mentioned the remarkable formal resemblance between the structures of these steroids and that of the macrocyclic musk civettone (XXXII).

Recently prof. Kloek of Utrecht University, in the course of his work on psychiatric aspects of odor perception (16) collected a large series of steroids and he was kind enough to allow me to study the odor of these materials. All compounds were evaluated by a team of professional perfumers and their opinion were condensed into a few characteristic terms.

The steroids were only available in extremely small quantities which did not permit further purification and we have to accept the risk that the observed odors are influenced by traces of impurities. However, since all were obtained from the sample collections of well-known institutes and since they have roughly the same odor pattern (although part of them were isolates and the other part synthetics) this risk seems to be very small.

Table I

Androstane derivatives.

Name	Structure	Intensity	Quality
5 α-Androstan-3β-ol		weak	Musk, woody, urine, sweat.
5 β-Androstan-3β-ol		weak, one strong	Musk, amber, meat extract.
5 α-Androstan-3α-ol		strong	Musk, sandalwood, urine.
5 β-Androstan-3α-ol		weak to strong	Musk, woody, urine.
5 α-Androstanone-3		strong	Musk, urine.
Androsten-5-ol-3β		weak to strong	Musk, woody, urine, sweat.
Androsten-4-one-3		weak to strong	Sandalwood, urine, sweat, castoreum.
5 α-Androsten-16-ol-3β		strong	Urine, sandalwood.

Of the 33 steroids examined no less than 23 were found by all or part of the observers, in some cases only by one, to have odors more or less strongly associated with musk.

The observed odor intensities vary considerably not only between compounds of approximately the same molecular weight but also for each compound between observers. Often a compound which has a strong odor for one observer is practically odorless for another.

In table I the data for a number of androstane derivatives with a functional group at C3 are summarized.

The 4 androstanols all have musk associations. The odor intensity of both 3 α-compounds is higher than that of the corresponding β-epimers. This is in perfect agreement with Prelog and Ruzicka's (15) observation on the 5 α-androsten-16-ol-3 epimers. In our work Ruzicka's 3 β-epimer was found to have a rather strong odor, without any musk associations.

Replacement of the hydroxyl group by a keto group has very little influence upon the odor in this series. Introduction of a double bond in the position 16 increases the intensity but destroys the musk odor while double bonds in 4- and 5-positions have little influence.

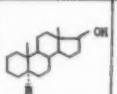
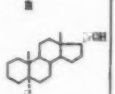
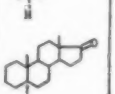
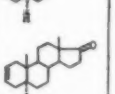
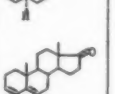
Androstane derivatives with a functional group at C17 (Table II,) have a weaker average odor than their C3 analogues although this reversal of the profile does not have much influence upon the quality of the odor. Also in this series, most compounds have musk odors.

3. A poor accessibility of the functional group increases the influence of random orientation and weakens or destroys the odor.

This is suggested by the rapidly decreasing odor-intensities in the musk series XXXIII and XXXIV with increasing size of the alkyl group R.

Table II

Androstane derivatives.

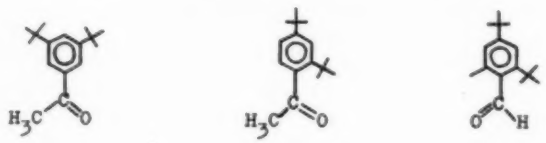
Name	Structure	Intensity	Quality
5 α-Androstan-17β-ol		weak to strong	Amber, cheese, phenol.
5 α-Androstan-17α-ol		weak	Musk, civette, woody.
5 α-Androstan-17-one		weak	Musk, woody, urine.
5 α-Androstan-2-one-17		weak, one strong	Amber, musk, civette, woody, urine.
Androstadien-3,5-one-17		weak	Musk, woody, urine.

XXXIII XXXIV

Figure 20

The increasing group R tends to screen the carbonyl group without having a function as a profile group.

A more interesting example is presented by the three isomeric carbonyl compounds XXXV-XXXVII.



XXXV XXXVI XXXVII

Figure 21

XXXV is a musk of considerable strength. At the same time the oximation velocity of the carbonyl group is normal for an aromatic ketone. The isomeric ketone XXXVI is completely odorless and does not form an oxime. According to the P.F.G. concept the carbonyl group which is effectively screened by the tert.butyl group, cannot be responsible for a reasonable affinity; the orientation pattern degenerates and the compound has no odor. The objection that the 2,4-di.tert.butyl phenyl-profile is not the same as the 3,5-ditert.butyl phenyl-profile cannot explain this phenomenon because the isomeric aldehyde XXXVII which oximates slowly is a musk of moderate strength.

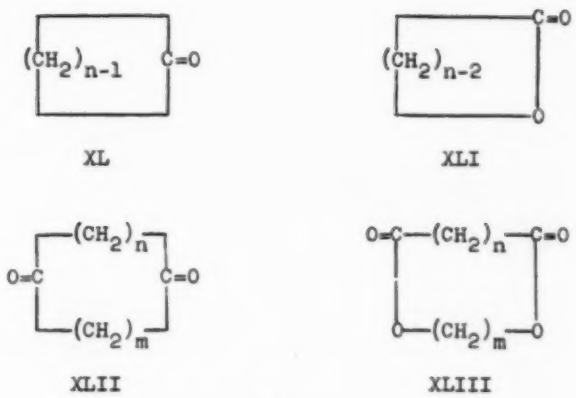
XXXVIII XXXIX

Figure 22

Of the two tricyclic ketones XXXVIII and XXXIX described by Carpenter (17), the first with a carbonyl group of normal accessibility, is a musk, whereas XXXIX in which the carbonyl group is screened by a quaternary carbonatom in orthoposition is odorless.

4. The introduction of a second, equivalent functional group has an influence which is dependent on its position; in juxtaposition the two groups can cooperate; with increasing distance, competition between both results in a rapid drop of the odor intensity.

This effect is clearly demonstrated in the macrocyclic series.



XL XLI

XLII XLIII

Figure 23

Macrocyclic ketones (XL) and lactones (XLI) are strong musks. Introduction of a second keto group (XLII) destroys the odor. Introduction of a second ester group in a lactone (XLIII) results in the formation of a good musk when both groups are close enough together to cooperate as one functional group. Ethylene brassylate (XLIII; n = 11; m = 2) is a good example. The odor intensity decreases rapidly as the distance between both ester groups increases. Cooperation changes into competition and the orientation-pattern degenerates.

Conclusion

I am well aware of the fact that nothing has been proved by what I have told you. My only intention was, to demonstrate that our experience with the facts of olfaction can be understood better if we look at the molecule of an odorant not as a machine but as a sculpture, not as a chemical reagent but as an object with a most significant shape and a most significant orientation.

The story breaks off in the middle and we can only wait patiently until someone takes it up again to write the next chapter or to rewrite the first. Let us hope that this will be done by physicists, chemists and physiologists in close cooperation because only then we may expect to make real progress.

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Discussion of Papers

DR. WILLIAM AMOLS, Moderator

Question: *Dr. Engen, I have always thought that the study of odors was related, at least in theory, to the study of a foreign language. Now it normally takes three or four years, when you are living in the country where you are studying the language, to learn several thousand words. In the experiment you so well described your pupils learned to identify about 16 different odors of chemicals in the course of 8 weeks, and I am wondering where the study of a foreign language differs in quantity or quality, or is the sensory process entirely different when studying words and sounds than when studying reactions and identification of odorous molecules?*—RAOUL PANTALEONI

Answer: I think it is very clear that the amount of learning which is going to be involved will depend on motivation (the interest the person has), and when you are in a foreign country you are much more motivated to learn the language. As to the learning of odors by my subjects, they were involved to the extent of a comfortable job that they would rather keep than to do dishes in the cafeteria. They were interested but not extremely so, I'm sure, and I think this is absolutely the main difference. If they had a chance to become perfumers as their main occupation and were given some more time, they could change drastically. All that I tried to determine was how they would perform in this fairly reasonable everyday life situation. But I am sure that I don't get anywhere close to the limit of their ability.

Question: *Dr. Tucker, I have been working with human beings using olfactometers for the past nine months concentrating on the musk odor. All of my subjects are highly selected, and are not like Dr. Engen's people, they really are the best, most odor-sensitive I can find and then I train them. Before and after a 30 minute session, I examine their airways by means of a nasal speculum and to my amazement, I notice there is a greater patency (dilation) in the airways following the 30 minute period with certain Musks, just which ones, I can't say offhand. My question is, have you observed any facsimilies of this phenomena where certain odors (I know you have not been using the same ones that I did) have increased the patency in the cold blooded vertebrates you have worked with?* —DR. JOHNSTON

Answer: Yes, in the case of the tortoise and the chemical Benzylamine you always get this effect. This is true for others, too, and we don't have to stay with cold blooded animals. We can get the same effect with mammals—as observed when working with rabbits. If you would give me the information I would be very interested in knowing the Musk odors that do this. I would like to work with some of them.

Question: *Dr. Amols, one is aware of a correlation between disease and odor. Would you as a practicing physician be able to comment on this, and further, has anyone ever expanded on this theory as a means or as a help in diagnosis?*—Jacques Masson

Answer: Oh, yes, the sense of smell is employed by practicing physicians along with the senses of sight, sound, feel and touch to a very great extent, and there are characteristic odors in certain disease states. The fruity odor of acetone on the breath of the patient with diabetic acidosis is a classical example. The characteristic odor of the breath in the patient who is in renal failure. Uremic, people with intestinal obstruction, can have the fecal odor to their breath. Certain infections will carry typical odors, and astute physicians can appear on the floor of a hospital and know that there is a lung abscess some place on that floor. Not only in diseased states are odors present and utilizable, but in various physiological states that do not constitute disease. People often complain that when they are nervous their perspiration smells. Other people when they are tired will have an unpleasant odor, often about their feet. So it is a fact that there is an appearance of odor in various patho-physiological and actual disease states which can be detected.

Question: *Dr. Amols, you said at the beginning of your discussion that the odor of a product depends not only on the product itself but also on the intelligence of the person who smells the product. Do you believe, as I do, that various people smell the same chemical differently? In other words, would several perfumers mix different chemicals to achieve exactly the same odor? That because of this difference in conception one perfumer can never follow the formula of another by reason of the difference in appreciation?*—Ernest Shiftan

Answer: The statement I made at the outset was that smell or odor was a characteristic not only of the substance but also a characteristic that is shared by the intelligent being who perceives and discriminates and then, perhaps, communicates that odor. Therefore, it is a shared property. Now, we have no way of comparing inner experiences. We know that in life certain colors have characteristic wave lengths, and that in terms of objective measurement we can be sure we are dealing with a pure color when we deal with a certain wave length. We don't really have any effective way of knowing that subject "A" perceives the color in exactly the same fashion that subject "B" does. We do know that there are tremendous individual variations and that indeed, in the extreme, some people perceive color in a manner which is so different as to be measurable, by various techniques. There are color-blind people in various grades and shades. I suppose that we know that also in sound there are tone-deaf people. But I suppose it isn't too far afield to assume that there might be, in the field of human variation odor insensitive people and people who perceive odors somewhat differently . . . subjectively . . . which is probably one of the problems in communication between perfumers.

Question: *Dr. Amols, I did not mean that some people smell better and others not as well—I mean that they actually get a different impression from the same chemical.*—Ernest Shiftan

Answer: Entirely different—this is what I am trying to imply. Some people will see a vivid hue only as gray or some shade of gray and they will respond to this as though they were responding to a more deeper hue. I am sure that some people will smell or sniff an odor and get a subjective experience from this which is deeper, more profound, or richer if you like, than another person who will be dealing with the same thing. And they will be appreciating it not more sensitively or less sensitively, but differently from each other.

Question: *This is primarily directed to Dr. Engen though it would be interesting to hear from the other speakers whether they have any experience on the following. In your odor evaluation tests have you found a significant difference when employing an all male panel against an all female panel, or either one against a mixed panel?*—Dr. Oliver L. Marton

Answer: I couldn't really tell the males and the females apart by looking at the results. I was not struck in any way at all by a performance difference between the sexes. I can say that the best evaluation I ever received was from a male.

Question: *Dr. Engen, from your description of*

the experiments, I gather that the subjects in the smelling booth did not have comparison standards with them and had to rely on their memory for identification of the odors. Was it your intention to test the absolute ability of your subjects to distinguish odors qualitatively and quantitatively, i. e. type of odor and intensity of odor based upon the physiological ability to differentiate? Or were you testing their odor memory, thereby to correlate their ideas of the odor by memory with the things they had smelled previously? In other words, if you were testing discriminatory ability rather than memory, and if the subject had 100 or 500 different standards in the booth for comparison, I imagine they could have scored much higher, practically 100%. Is that correct?—Dr. Theimer.

Answer: Yes, that is quite correct. It was from memory. You might think of this as an attention span experiment as well, but it is true that if they had more categories, more experience, they could have done better. This, of course, was partly what I wanted to find out. How do people react without any special training? Now one thing that relates to several of the questions that have come up, such as the last one, is that results of this kind, whenever used on human begins, will have a great number of artifacts involved. It is easy to show, for instance, the difference between males and females in the case of color. In my laboratory I once checked this out. I did the same experiment with colors and found that females are always a bit better than the males in identifying colors. Why? They have more names to start with; I was trying to keep that constant in my experiments as much as I could; but it is definitely a factor.

Question: *I have two questions for Dr. Beets. In the late '30's Dyson published a theory which tries to correlate the vibration frequencies, Raman spectra, to the quality of odor. How do you stand on that, or could it supplement your picture of geometrical matching? The second question is, do you have any thoughts on the mechanism by which this matching actually produces the electrical signal in the nerve?*—Dr. Dravnieke

Answer: In the first place I know Dr. Dyson's theory on the relationship between odor and Raman spectrum. This point was recently discussed very extensively by Prof. Thompson of Oxford University at a symposium in Geneva and it was concluded that all theories in which there is no material contact between the receptor surface and the alien molecule (the stimulant molecule) is assumed of no value. It is so, of course, that a Raman spectrum represents a number of structural details of an odorant molecule, and although it is rather farfetched, there could very well be a relation between the Raman spectrum, the IR spectrum and the odor.

When you put a structure of a molecule on paper with all its conformational details correct, then you have at the same moment all its properties: chemical, physical and psychological, and of course, one other element, that is the structure correlates the total properties. There is of course, a relation between the total and the individual properties. I consider it completely fruitless to follow this route, to follow this suggestion, as a way to increase our knowledge in the field of olfaction.

As to the second question, being an organic chemist and not a physiologist, I have kept myself far removed. There are, of course, quite a number of very interesting theories on this mechanism and I would mention in the first place the mechanism proposed by Davies and Taylor on the analogy between the stimulating mechanism of olfaction and haemolysis. But I don't think it is my task to propose to add a new theory to the number of already existing theories which are still waiting for experimental support.

Question: *Dr. Beets, I would like to indicate that my views concerning these last two questions are essentially those of yours. I think that, among the various theories of olfaction, the theories of Davies and Taylor and Mullins in this country are essentially similar among the better theories. There are many physical properties that can go along structurally in the molecule or a molecule series. You mentioned something that has interested me for some time when you said that the acetylcholine molecule, or the acetylcholine receptor for it, was at least suspected of having something to do with odors. I wonder if you would be willing to speculate just a little on the connection between acetylcholine and the musks which have an acetyl group at about the same distance from a tertiary amyl group; this same having the same shape as trimethylamine?*—Dr. Tucker

Answer: Well, as you know the quaternary ammonium group in acetylcholine is mainly responsible for the efficacy of the molecule insofar as it is analagous to the parts I have assigned to the tertiary butyl group in the musk field; the tertiary butyl group adds to the bulkiness of the structure. It is, of course, also true that there is a similarity between the quaternary ammonium group and the tertiary butyl group but I think it would be very speculative to base a theory upon this similarity. It is a fact that when we replace the tertiary butyl group by a higher tertiary alcohol group the odor character does not change but the odor intensity rapidly decreases. Similar work has been done on acetylcholine where the quaternary amino group has had the methyl groups replaced by higher alkyl groups and then we see a similar effect, but I do not know whether this is a sufficient basis to assume a real similarity between these two specific groups.

ABSTRACTS from the SEMI-ANNUAL SCIENTIFIC MEETING Society of Cosmetic Chemists May 12, 1961

The Contribution of the Organic Chemist to the Cosmetic Industry

Doctor Jack Goodman
The Toni Company

An outline of the over-all position of organic chemistry in the cosmetic industry. The functions of the organic chemist in such areas as synthesis, evaluation, product development, etc., are explored. Included are examples of the scope and complexity of cosmetic organic problems with special emphasis on synthetic approaches. The importance of the contributions by this branch of chemistry is detailed.

The Contribution of the Chemical Engineer to the Cosmetic Industry

Mr. Theodore Swenson
Helene Curtis Industries, Inc.

The paper first defines chemical engineering and various functions within that field. An explanation of practical applications of a general nature is included. The work given the chemist and chemical engineer is compared and differentiated. Emphasis is placed on the utilization of chemical engineers within the cosmetic industry for process development and project engineering: typical examples are explained in some detail. Other sections include safety applications and future possibilities.

All of these papers will be published in the Journal of the Society of Cosmetic Chemists. Subscription to the Journal is $6.00 to members, and is included in the dues to the Society. The subscription price to non-members is $18.00 per year in North America, and $18.90 to other areas of the world.

The Journal is published nine times each year, during January, February, April, May, June, August, October, November, December. Information relative to subscriptions or memberships is available from the office of the secretary, Mr. Robert A. Kramer, 250 East 43rd St., New York 19, N. Y.

Instrumentation in the Cosmetic Laboratory

G. M. Leigh and A. P. Kent
Colgate-Palmolive Company

The instrumental armamentarium of the cosmetic laboratory has been augmented in recent years by more complex apparatus and affords with high precision and greater speed useful information which, in some cases, was previously unobtainable. Spectral and chromatographic techniques have enjoyed particularly rapid growth. Several examples are given of the range and versatility of these methods in the modern cosmetic laboratory.

Physical and Chemical Properties of Shellac and its Derivatives

Mr. Herbert Cockeram
Acme Shellac Products Company

A review of present-day knowledge of the chemistry of shellac, its derivatives and constituent acids. The most recent accomplishments and objectives of research in India and America is reviewed, and the future of shellac development assessed.

Promising Areas of Cooperation Between the Committee on Cosmetics of the American Medical Association and the Society of Cosmetic Chemists

Joseph B. Jerome
Committee on Cosmetics

Careful consideration of the interests of the many diverse groups currently concerned with various aspects of marketing cosmetics indicates that they all have one fundamental goal. This can be summarized quite briefly as the marketing of safe cosmetic prod-

ucts. Another important point is the efficacy of the product. It should have the effect it is claimed and expected to have.

The various methods by which the Committee on Cosmetics and the cosmetic chemists can cooperate in mutual education would seem to involve:

a. A review and evaluation of data available from studies which have already been made on skin and hair with emphasis on cosmetic applications;

b. The establishment of recognized evaluation procedures which are to be followed in the assessment of different classes of cosmetic materials.

c. Further advances toward the establishment of standard nonproprietary nomenclature for cosmetic ingredients.

The existence of a number of areas in which fruitful basic research work can be done, and the fact that the future growth of the industry could very well come from the basic knowledge developed in these areas suggests that industry should increase its support of basic research activities within and outside its own laboratories. It would be appropriate for industry to ensure prompt release for publication of all research material which is no longer of immediate commercial significance. Experience in other areas of scientific research indicates that far more can be gained by the sharing of the results of research than by restricting the availability of such information.

A productive area for fundamental cooperation would appear to lie in the education of the public as to the appropriate use of cosmetics as part of the normal daily care of the hair and skin. The present sporadic and limited exposures to reliable information of prospective lifetime customers is inadequate.

The Contribution and Role of the Pharmaceutical Chemist in the Cosmetic Industry

Richard E. Faust
Cuticura Laboratories

Through the years there has been a close relationship between pharmacy and cosmetic technology. Now, today, with the greater incidence of pharmacologically active agents in cosmetics, this kinship becomes even more important. The academic training a pharmaceutical chemist receives provides him with a broad understanding of the physical, biological and chemical sciences which represents a most suitable background for work in cosmetic research and development. Over one-third of the colleges of pharmacy offer courses in cosmetics and considerable research of interest to cosmetic chemists has emanated from pharmacy schools.

A survey shows that pharmacists are employed by the cosmetic industry today on a rather limited scale. In the complex of activities that constitutes the modern cosmetics plant, these pharmaceutical scientists are living in a society of specialists, most of whom by the nature of their training may be more highly skilled in a particular area. In the actual formulation of the cosmetic product, however, the pharmacist can contribute his unique talents and compounding skills, for in many ways these are a part of what has been called the "art of pharmacy."

Because of the specialization and departmentalization which comes with growth and the increasing complexity of basic sciences, it is entirely appropriate and necessary that research in cosmetic science employ many specialists. However, it is possible that we can go too far in the direction of specialization, so that the investigator lacks versatility and a broad appreciation of the many over-all complex problems associated with the development of a new cosmetic product. In smaller laboratories, especially, where fewer than six persons are engaged in research and development (and it has been estimated that over half the cosmetic companies fall in this category) it is essential that technical personnel have a comprehensive understanding of the basic sciences. Also they must have a degree of flexibility in meeting problems which require a broad appraisal of the entire project or program. The basic curriculum in pharmacy, which includes courses in bacteriology, pharmacology, pharmacognosy, organic chemistry, and bio-chemistry, in addition to the many subjects covering various aspects of pharmaceutical compounding and dispensing, contributes to producing a well-rounded and versatile research chemist in the cosmetic laboratory.

It is hoped that the cosmetic industry will begin to explore more fully the many ways in which the pharmaceutical chemist can contribute to successful cosmetic research, development and production.

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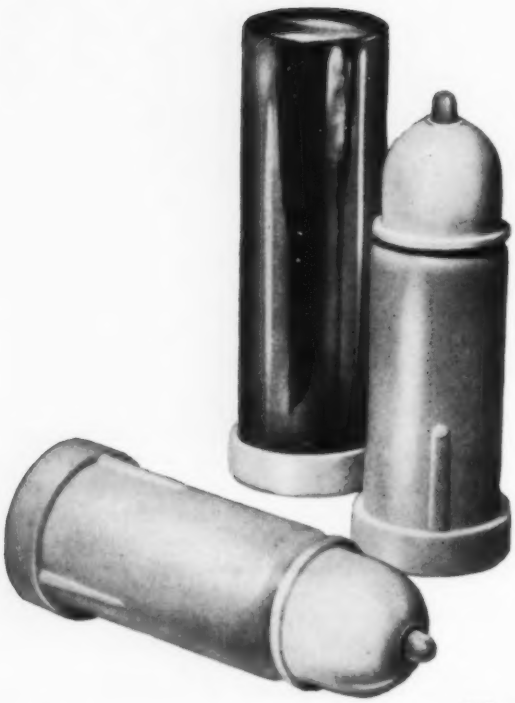

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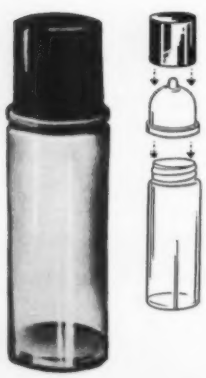

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Production Information

BY WALTER G. FREDELL

WHETHER A PRODUCT is cosmetic or pharmaceutical, a check list can be of great assistance in determining a course of work, note progress on a project, and assist in seeing that no important points are overlooked. Over a number of years when discussions of product suggestions, and work on some of the suggestions has been planned, the following outline has evolved.

Check List for New Product Information
(Where possible, state in terms of known items)

1. **Classification?**
2. **Chemical Nature of Product?**
3. **Physical Nature of Product?**
4. **Perfume or Flavor Characteristics?**
5. **Color Characteristics?**
6. **Uses and Method of Application?**
7. **Type of Package?**
8. **Stability?**
9. **Cost?**
10. **Control?**
11. **Availability of Ingredients?**
12. **Toxicity and Safety?**
13. **Competitive Products?**
14. **Relative Activity of Product Usefulness?**
15. **Equipment?**
16. **Miscellaneous?**

Before starting work on a possible product, some items which are not actually technical in nature but which have a bearing on, or interest in, the product must be considered. The length of the list under item 16, miscellaneous, is variable and here one should ask: "what else do we need to know about this product?"

One item hereunder, could be *sales potential*. To illustrate this point, I cite an actual case. Material in this article has been presented to various luncheon groups (Rotary, Kiwanis, Lions, etc.). I selected a cosmetic or pharmaceutical item of some common interest as an example to illustrate the importance of each item in the check list. On one occasion with more than fifty men present, I was talking on lather shaving cream, and asked for a show of hands from those who were users of lather shaving cream. Not a single hand was raised. More extensive market surveys than this are needed, but this illustrates *sales potential*.

Another item is *legal considerations*. In the field of pharmaceuticals, Food and Drug approval of new preparations is required. The answer to similar questions about cosmetics is also needed. Answering the questions of the check list in the laboratory is a good start toward a new drug application.

It is to be understood that answers to all items will not be given if the outline is used for a product suggestion. Sometimes only the classification or descriptive title serves for a product suggestion but additional information should be presented if available.

If interest is shown in a suggestion and some work is contemplated, a preliminary discussion and recording of aims is invaluable to all workers on the problem. This practice eliminates unnecessary work. The formulator, evaluator, and analyst must know if there is to be a particular active ingredient, the physical properties to be desired and the manner in which the product is to be used. With preliminary formulations under way, ideas on color and perfume must be finalized as well as the type of package.

In discussing any of the points, examples should be noted in terms of commonly known items at hand. For example, the physical state may be an opaque liquid with the pour characteristics of skimmed milk; or the color should be a shade of red like the chair coverings in the conference room. This is fine if characteristics can be defined very clearly, otherwise the formulator must make various products with different properties.

As an example of a development problem, let us consider that a product desired is an antiperspirant-deodorant. With this in mind, we become interested in item 2–"Chemical nature of the product." A literature search turns up an excellent review with references by Dr. E. Klarmann (1). From the literature, and contacting suppliers of chemicals familiar with what has been used, we accumulate a list of active astringent chemicals, antiseptic chemicals, and others said to be active agents. Maybe we have ideas of our own on new possible active agents. At this point one is thinking also of item 14–"relative activity of product usefulness"–so as to ask suppliers what is the activity of their chemicals for the intended purpose. Also leads are available from them on test methods for evaluating the individual chemicals as well as

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the final product when it is produced. The vehicle to carry the active ingredient or ingredients is considered after giving thought to some other items.

Item 6 mentions "method of application". Noting "competitive products", item 13, on the market one finds creams, clear liquids, plastic squeeze bottles for spraying a product in the axillae, and roll-on products. One should consider any new and novel ideas that may present themselves.

In drawing conclusions in the previous paragraph, item 7, "type of package" is involved. Let us for this example suggest an aerosol spray. Note how this decision crystallizes thoughts on the product. Regardless, all of the points stated will have had to have been covered. Now the check list can be approached in numerical order with pertinent points clear to formulator, evaluator, and analyst.

1. Antiperspirant-deodorant defines clearly what is desired by way of a product.

A check with suppliers of the newer astringent salts used in antiperspirants reveals that compatible concentrates can be produced with specially denatured alcohol as a solvent but a problem arises when it is packaged in an aerosol. (See item 7, below, for a comment on the problem.)

The antiseptic agents Hexachlorophene, Bithionol, Anobial, and Hexetidine lend themselves to compatible formulas. One such formula is as follows:

Concentrate for Aerosol

Hexachlorophene	0.4 g
Glycerine U.S.P.	1.0 g
Perfume	1.0 g
Deltyl Extra	1.0 g
Dipropylene Glycol	5.0 g
SDA No. 40	91.6 g
	100.0 g

Aerosol Product

Above concentrate for Aerosol	70.0 g
Propellant (60% Freon 114; 40% Freon 12)	30.0 g

2. Active ingredients to produce the above product are to be compounded in such a way that they are compatible for dispensing in an aerosol.

3. Most possibly a liquid to be compatible with aerosol propellents. (Powders are packaged in aerosols but generally we might not consider them suitable for this type of product). The formulator must struggle with this item to produce a suitable product.

4. Both men and women could use the product so the perfume should be agreeable to both or, on the other hand, an odorless product may best serve the purpose.

5. Since the product is an aerosol, in an opaque container, no color need be added as it will never be seen.

6. The product is sprayed in the axillary areas. Should it be rubbed in after spraying on, or just allowed to dry by itself? Evaluation of the product with and without rubbing should determine the best method of application and be stated in directions to the consumer.

7. The nature of the ingredients may indicate that a glass package is preferred over metal because of the corrosive action of the ingredients.

As stated above, a problem arises with concentrations of aluminum tried in aerosol packages when

this concentration is at a level to have antiperspirant activity. Under use conditions, the solvents evaporate so rapidly that the salts crystallize and the valve becomes clogged. This clogging problem is a mechanical one and, until some solution is found, this type of package is not suitable.

Under these circumstances, we must conclude that we must alter our thoughts of the product because, under present conditions, we seem to be able to produce a deodorant product but not one with antiperspirant activity in this type package.

8. Stability of the formulated product will have to be determined in the laboratory.

9. At this stage, a preliminary materials cost should be determined and this includes the package; that is, the glass container, dip tube, and valve. This also indicates that the formulator should have some idea of cost of materials with which he works.

10. For any product produced, control information is required. In this case, spray pattern, quantitative determination of active ingredients, and statistical sampling fit into the picture and will have to be worked on prior to actual production. This is still development work in the hands of the analyst.

11. Before going all-out on a new product, it is advisable to know that your ingredients are available in the quantities required. From a development standpoint, one often works with such a new ingredient that it is in the development stage and not available in quantity. If the product is to be produced in a foreign country, what about the availability of ingredients?

12. Suppliers ordinarily can furnish data on the toxicity and safety of active chemicals. However, data must be acquired on the final product that may be marketed. This data may be accumulated by the evaluator or a consulting laboratory.

13. Competitive products are of interest to check advantages of application of the new product and also activity.

14. Evaluation of the usefulness of the product is most important. Using tested evaluation procedures, does the product do a job? The Society of Cosmetic Chemists has published tentative methods for evaluating antiperspirant and deodorant effects.

Under item 7 we seemed to rule out an antiperspirant product and concentrated on a deodorant product. The literature notes that some studies were made on deodorization of already odorous axillary areas. Of the antiseptic agents mentioned above, Hexachlorophene was included in the studies and found to be effective. Any formulation should be tested for this activity and duration of activity in the absence of a perfume.

15. The struggles with original formulative work should help answer the question of type and chemical nature of equipment suitable for production of the product. The formulator should have this point in view in his work.

16. What other problems have come up in work on the product? As new problems arise, they should be noted and enumerated here. Most all questions have been raised by considering the preceeding

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points individually, but something new can always occur.

Conclusion

With the above recorded information, marketing, advertising and legal areas have a full picture of the product and can carry the ball from there. Regardless of the status of the project . . . new, under development, or old with thoughts of additional work for improvement, a few more test questions can be listed.

1. Where are we?
2. How did we get there?
3. Where are we going?

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(1) Klarmann, Emil G.: "Deodorants and Antiperspirants" Part 1, Drug and Cosmetic Industry **81** 36, 1957. Part 2, Drug and Cosmetic Industry **81** 177, 1957.

TGA Conferees

Paul Z. Bedoukian, Mrs. Gertrude M. Sa Voie, Compagnie Parento, Inc.; **J. P. Leroux,** Rhodia, Inc.

Edward G. Merritt, Chas. Pfizer & Co., Inc.; **William A. Kessel,** Atlas Powder Co.

Rudolf R. Detz and **Thomas Biallo,** Camilli, Albert & LaLoue, Inc.; **Louis J. Bollinger,** Perfumery Associates, Inc.

1. **George H. Blake,** Givaudan-Delawanna, Inc.; **Jesse Starkman,** Gillette Safety Razor Co.
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3. **Ben Woods,** Avon Products; **Owen G. Carpenter, Jr.,** American Alcolac Corp.; **Herb Edelstein,** Bonat Products.
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Financial News of

by Edward A. Jones
Research Associate of Mitchell, Hutchins & Company

HELENE CURTIS IN MAY announced the planned acquisition of Pyramid Rubber Co. of Ravenna, Ohio. Pyramid makes the Evenflow line of bottles, nipples and other baby products. The acquisition is to be accomplished through an exchange of stock and does not involve a dilution of earning power. This is a major forward step for Helene Curtis which also acquired Plastics Products for cash earlier in the same month.

Formerly traded over-the-counter, Helene Curtis class "A" common stock was listed on the New York Stock Exchange on April 10, 1961. The symbol is HC. On April 19, 1961, Max Factor class "A" common stock moved from the American Stock Exchange to the New York Stock Exchange. The symbol is FAC.

A 3-for-1 stock split for Lehn & Fink became effective April 20, 1961. A 2-for-1 stock split for Revlon became effective April 19, 1961. Nestle-LeMur has declared a 100% stock dividend payable August 10, to shareholders of record July 20. The cash dividend is expected to be increased by one-third. Except for Nestle-LeMur, all financial data in the table is adjusted accordingly.

Sharply higher prices for cosmetic and personal care product company stocks has encouraged more initial public and secondary offerings. Notable are:

(1) 400,000 shares of Max Factor sold at 56-¾ per share in April 1961. Half was for the company account and half was for the controlling Factor family.
(2) last December, there was a 130,000 share secondary offering by Revson and Lochman, major stockholders.
(3) an initial offering of Charles of the Ritz on April 28, 1961. This was a secondary involving 215,000 shares, 21.5% of the outstanding stock.
(4) Stephan, a men's barber shop-hair tonic business, offered 150,000 shares at $4 per share in October 1960. The stock now trades on the American Stock Exchange.
(5) An initial offering of Alberto-Culver came at $10 per share in early April. Involved were 155,000 shares.

It is anticipated that an initial offering will be made this year of Lanvin common stock. Lanvin sells a high fashion fragrance line. As disclosed in a law suit, the company's 1959 sales were $14 million in 1959 and are believed to have risen to $16 million last year. The profit margin is estimated to be one of the best of the companies reviewed.

of the industry

Annual Comparison

	Sales			Net Income			Margin		Earnings per Share		
	1960	1959	Percent Increase	1960	1959	Percent Increased (Decreased)	1960 Net Income to Sales	1959 Net Income to Sales	1960	1959	Percent Increased (Decreased)
	—millions—			— (000) —							
Alberto-Culver (1)	$ 14.9	$ 10.4	43.3%	$ 516	$ 123	319.5%	3.5%	1.2%	$ .53	$ .13	315.4%
Avon Products	168.2	141.9	18.5	17,118	14,395	18.9	10.2	10.1	1.79(7)	1.50(7)	19.3
Beauty Counselors	11.8	9.8	20.4	1,162	977	18.9	9.8	10.0	1.58	1.34	17.9
Charles of the Ritz (2)	14.4	13.4	7.5	1,100	900	22.2	7.6	6.7	1.13	.93	21.5
Chesebrough-Ponds (3)	70.2	66.3	5.9	4,517	4,030	12.1	6.4	6.1	1.51	1.38	9.4
Helena Rubinstein	31.1	27.2	14.3	1,701	1,425	19.4	5.5	5.2	3.33	2.82	18.1
Helene Curtis (4)	54.0	48.1	12.3	3,230	2,490	29.0	5.9	5.2	1.58	1.23	30.1
Lanolin Plus	13.4	12.2	9.8	1,061(6)	1,457(6)						
Lehn & Fink (5)	34.4	32.6	5.5	1,466	1,317	11.3	4.3	4.0	1.45	1.31	10.6
Max Factor (9)	59.2	53.2	11.3	4,024	3,725	8.1	6.8	7.0	1.76	1.63	8.0
Nestle-LeMur	15.9	13.9	14.4	779	678	14.9	4.9	4.9	.96	.90	6.7
Revlon, Inc.	136.4	124.9	9.2	11,321	10,837	4.5	8.3	8.7	2.16	2.09	3.2
Shulton	50.1	43.7	14.6	3,433	3,754	(8.6)	6.9	8.6	2.70	3.07	(12.1)

First Quarter Comparison

	Sales			Net Income			Margin		Earnings per Share		
	1961	1960	Percent Increase	1961	1960	Percent Increased (Decreased)	1961 Net Income to Sales	1960 Net Income to Sales	1961	1960	Percent Increased (Decreased)
	—millions—			— (000) —							
Alberto-Culver	$ 4.7	$ 3.7	27.0%	$ 80	$ 254	(68.5%)	1.7%	6.9%	$ .08	$ .27	(70.4)
Avon Products	33.1	31.9	3.8	2,632	2,314	13.7	8.0	7.3	.27	.24	12.5
Beauty Counselors	3.1	2.9	6.9	384	364	5.5	12.4	12.6	.52	.50	4.0
Charles of the Ritz	N.A.	N.A.									
Chesebrough-Ponds											
Helena Rubinstein (8)	17.2	16.9	1.8	730	786	(7.7)	4.2	4.7	1.43	1.55	(8.4)
Helene Curtis	N.A.	N.A.									
Lanolin Plus	N.A.	N.A.		191	97	97.0	N.A.	N.A.	.16	.08	100.0
Lehn & Fink	10.0	8.5	17.5	426	374	13.9	4.3	4.4	.38	.37	2.7
Max Factor	14.0	12.9	8.5	910	827	10.0	6.5	6.4	.40	.37	8.1
Nestle-LeMur	4.2	3.8	10.5	230	200	15.0	5.5	5.3	.28	.25	12.0
Revlon	33.0	29.9	10.4	2,690	2,535	6.1	8.2	8.5	.51	.49	4.1
Shulton	8.9	7.6	30.3	435	340	27.9	4.9	4.5	.33	.26	26.9

Footnotes for above tables:

(1) fiscal year ends November 30, above quarter ended February 28.
(2) initial offering was in April, 1960. Excluded from above data is Venus Pencil, which was purchased in November 1959. Venus Pencil had sales of $13.5 million in 1960 and $2.2 million in 1959.
(3) excludes Northam Warren, which was purchased for cash in late 1960 and is believed to have a volume of approximately $12 million. The company does not issue quarterly reports.
(4) fiscal year ends February 28 of the following year.
(5) fiscal year ends June 30.
(6) operating income, which is before a sizable deduction for amortization of patents. Tax loss carryforward precludes federal income taxes. These factors make earnings per share figures unsuitable for comparative purposes.
(7) Avon comparisons are somewhat distorted by a $.05 per share write-off against earnings in 1960 because of Cuba.
(8) for six months ended December 31 for 1960 and 1959 respectively.
(9) Max Factor earnings exclude non-consolidated Japanese subsidiary which in 1960 earned $.55 per share.
(10) includes Venus Pencil.
(11) includes Northam Warren.
(12) includes Pyramid Rubber.
N.A. Not Available

	Earnings per share 1961E	Price/earning ratio on 1961E	Recent Price	Traded	Shares outstanding (000)
Alberto-Culver	$ .25	100.0x	$ 24	O-C	950
Avon Products	1.90	53.7	102	O-C	9,548
Beauty Counselors	1.80	43.8	78	O-C	736
Charles of the Ritz	1.35	25.6	34½(10)	O-C	1,000
Chesebrough-Ponds	2.25	25.8	58 (11)	ASE	2,994
Helena Rubinstein	3.35	17.6	59	ASE	511
Helene Curtis	2.25	28.7	64½(12)	NYSE	2,035
Lanolin Plus	.75	21.3	16	O-C	1,163
Lehn & Fink	1.55	25.8	40	NYSE	1,130
Max Factor	2.15	26.3	56½	NYSE	2,288
Nestle-LeMur	1.25	41.6	52	ASE	815
Revlon	2.40	30.8	74	NYSE	5,245
Shulton	3.50	24.9	87	O-C	1,284

E—Estimated

PERSONALITIES

Anna J. Figsbee, (left), Avon Products, Inc. receives first "Cosmetic Career Woman of the Year" award from **Mrs. Kay Colton,** Morningstar-Paisley, Inc.

Miss Anna J. Figsbee, director of public relations for Avon Products, Inc., Rockefeller Center, New York City, has been awarded the "Cosmetic Career Woman of the Year" award. This year, Miss Figsbee celebrates her 60th year with the cosmetic firm. The award was given by Cosmetic Career Women, Inc., an organization of executive women in the cosmetic and allied industries. The CCW has headquarters at 1270 Ave. of the Americas, New York City.

Robert C. Ring is new sales manager of Duveen Soap Corp., Long Island City, N. Y. Ring is current president of the Cosmetic Industry Buyers & Suppliers Association.

J. G. FERGUSON

James G. Ferguson, vice president of the Laurens Glass Works, Inc., Laurens, S. C., is president-elect of the Glass Container Manufacturers Institute. Other officers elected include: **Roger H. Hetzel,** Armstrong Cork Co., first vice president; and **William M. Cameron,** Hazel-Atlas Glass division, Continental Can Co., second vice president. Board vacancies were filled by **S. B. DeMerell,** Anchor Hocking Glass Corp.; **R. H. Mulford,** Owens-Illinois Glass Co.; and **Dr. A. W. Wishart,** Knox Glass, Inc.

Kelco Company, manufacturer of refined algin products, recently announced the election of **Robert O. Davison** as vice president. Davison has been with Kelco since 1934 and will continue in his present position of manager of the firm's eastern division at 75 Terminal Avenue, Clark, New Jersey.

Robert S. Haley is now sales manager of the Vopcolene Division of Emery Industries, Inc. He was eastern sales representative for the Vopcolene Division before its acquisition by Emery. His area of responsibility will include sales of stearic, oleic, and other fatty acids, methyl esters, glycerine, and a variety of fatty derivatives through a group of direct field salesman.

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Coty's Executive Vice President **Jean Despres** was honored late last month by Coty for 40 years of continuous service to the firm.

In the presence of some 50 luncheon guests, (including fashion's Lilly Dache) honoring Depres, **Philip Cortney**, Coty's president paid tribute to him. Depres has long been identified as one of the spokesmen of the industry. He is president of the Fragrance Foundation, and past-president of the Toilet Goods Association.

Jean Despres, (left) Coty executive vice president, receives a commendation on his 40th Anniversary with the firm from **Philip Cortney,** president of Coty, Inc.

Sales manager for Union Carbide Olefins Company, New York City, is **Thomas W. Carmody,** recently appointed by that division of Union Carbide Corporation. Carmody joined Union Carbide Olefins when the company was formed in 1958 and prior to that was a sales engineer for the parent company.

Donald R. McLennan is now manager of the wholesale division of Yardley of London, Inc., and **Robert D. Spier** is manager of chain store sales. Spier was the firm's New England regional manager and will now fill the position previously held by Mr. McLennan.

Subsidiaries in Brazil and Argentina will be supervised for International Flavors and Fragrances by **Harry Fields** newly appointed area manager in South America. Fields will headquarter in New York City but will establish a base of operations in Rio de Janeiro for an indefinite period starting July 1st.

Jack V. Schurman is now manager-product development for oral products in Colgate-Palmolive Company's Research and Development Department. Schurman joined the company in 1950 as a research chemist.

The new director of manufacturing at Aerosol Techniques, Inc., Bridgeport, Connecticut, is **Harry W. Fillman,** former cost and budget manager for M & M Candies, Hackettstown, N. J. **C. Donald Schoonmaker,** will fill the position of plant engineer at ATI.

W. Howard Winters will serve Crown Cork & Seal Company, Philadelphia, Pa., as regional manager—midwestern region headquartered at the company's new sales offices at 5235 West 65th Street, Chicago.

Chief engineer for the Malmstrom Chemical Corp., Newark, New Jersey, **Thomas B. Richey, Jr.** has just been named vice president for production and development and elected to the board of directors.

Frederic Remington, Jr. moves from assistant superintendent to plant superintendent in charge of manufacturing for Peerless Tube Company, Bloomfield, New Jersey. **Thomas J. Lynch, Jr.** was promoted from office manager to assistant treasurer for the company.

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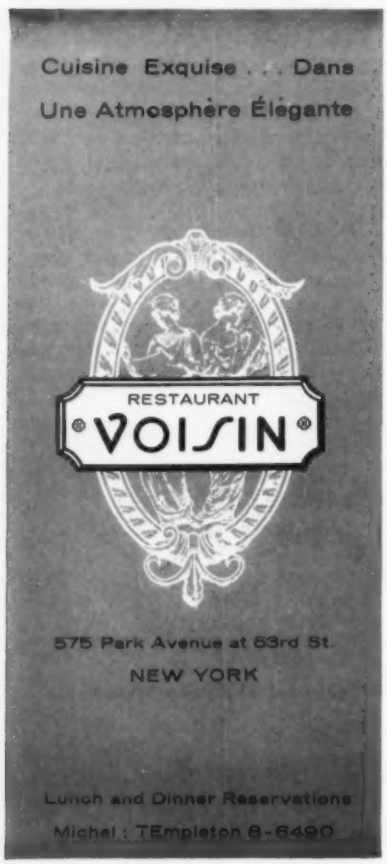
H. Bach Nielsen will supervise sales for Nichols Engineering & Research Corp., New York, in his new position of assistant to the general manager of the firm. Nielsen was formerly manager of the Nerco-Niro Spray Dryer Division of Nichols.

Stockholders of the Allen B. Wrisley Company, Chicago, Illinois, elected **Eugene F. Bertrand, A. C. Pelletier, A. C. Stoneman, George A. Evans, Earl Davis** and **Wrisley B. Oleson** to the board of directors at their recent annual meeting in South Gate, California.



Mrs. Mysie Emmet has joined the perfume staff of Perry Bros., Inc., New York City producer of perfume bases, essential oils, and aromatic chemicals. Mrs. Emmet is well known in the fragrance field. She was the first woman to be admitted to membership in the Society of American Perfumers in 1952.

Ultra Chemical Works, a subsidiary of Witco Chemical Company, New York City, recently named **William Carasik** technical director. Carasik will handle quality control, plant and process engineering, and technical services for the manufacturer of detergents and detergent chemicals.

Travelers

M. G. Couderchet, president of Charabot & Co., Inc., is visiting the parent company in Grasse, France. Plans are being made to extend operations in this country.

George Branigan, vice president of Ungerer & Co., in charge of the company's New York laboratories and New Jersey plant, recently toured South America's essential oil and aromatic chemical producing areas.

Obituary

Maurice Maubert, president-director general of P. Robertet et Cie in Grasse, France. Since 1905 he worked with raw materials for perfumes, and did considerable research on extraction processes. For his work, the French Legion of Honor was conferred upon him.

INDUSTRY EVENTS CALENDAR

June 20—**Chicago Perfumery, Soap and Extract Association** (Par-Busters' Golf Outing), Thorngate Country Club, Deerfield, Ill.

July 24-26—**American Oil Chemists' Society,** Short Course on newer lipid analyses, University of Rochester, Rochester, N. Y.

July 27—**Chicago Perfumery, Soap and Extract Association** (Par-Busters' Golf Outing), Itasca Country Club, Itasca, Ill.

Aug. 6-12—**18th International Congress of Pure and Applied Chemistry,** University of Montreal, Montreal, Canada.

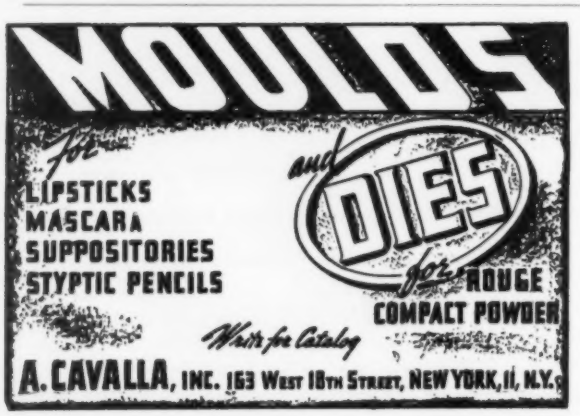
Aug. 17—**Chicago Perfumery, Soap and Extract Association.** Annual "swing party" and dinner dance, Glen Flora Country Club, Homewood, Ill.

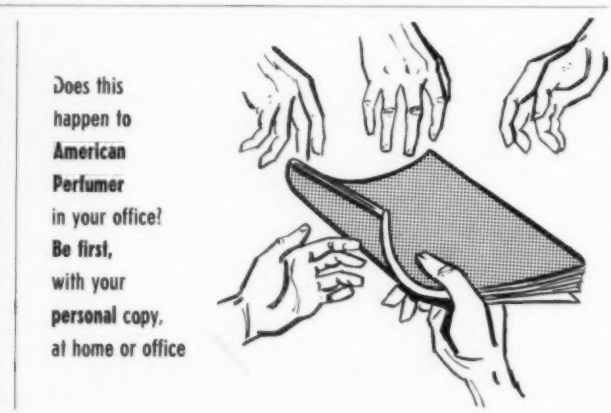
Oct. 18-20—**23rd Annual National Packaging Forum,** Biltmore Hotel, New York City.

Oct. 31-Nov. 1—**First International Symposium of Automatic Merchandising,** McCormick Place, Chicago.

Nov. 7-10—**Packaging Machinery Manufacturers Institute Conference-Workshop and Exposition,** Cobo Hall, Detroit, Mich.

Nov. 27-Dec. 1—28th Exposition of Chemical Industries, New York Coliseum, New York City.





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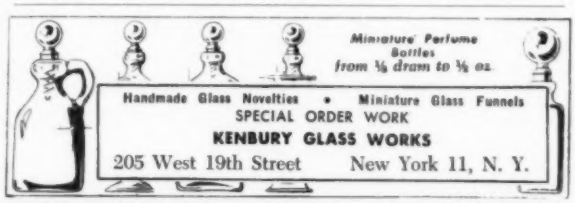
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Index OF ADVERTISERS

Aerosol Techniques, Inc. —
Albright & Wilson Mfg. Ltd. —
Allied Chemical Corp., General Chemical Division —
American Aromatics 14
American Cholesterol Products, Inc. 72, 73, 74
American Lanolin Corp. —
Anchor Plastics Co. —
Anderson, Carl N. —
Aromatic Products, Inc. —

Bedoukian, Dr. Paul 81
Bertrand Freres 7
Bios Laboratories, Inc. 80
A. Boake, Roberts & Co., Ltd. —
Bopf Whittam Corp. 75

Cameo Die & Label Co. 79
Camilli Albert & LaLoue, Inc. 82
Cavalla, Inc., A. 80
Celluplastic Corporation —
Charabot & Co., Inc. —
Chauvet & Co., Pierre 12
Chemo-Puro Mfg. Corp. —
Chimimport —
Chiris Co., Antoine —
Ciech, Ltd. —
Citrus & Allied Essential Oils Company —
Classified Advertisements 81
Clintwood Chemical Co. —
Colgate-Palmolive Company —
Continental Filling Corp. —
Coutin Associates 78
Croda, Inc. 69

Dehydag Products 22
deLaire, Inc. 76
Descollonges, Inc. —
Deutsche Hydrierwerke, G.m.b.H. —
Dodge & Olcott, Inc. 15
Dragoco, Inc. 1
E. I. duPont de Nemours —
Duveen Soap Corp. —

Emulsol Chemical Corporation —
Ertel Engineering Corp. —
Esperis, s.a. 68

Fairmount Chemical Co., Inc. 79
Felton Chemical Co., Inc. 25
Firmenich & Co. —
Fleuroma, Inc. —
Florasynth Laboratories 4

Fritzsche Brothers, Inc. —

Geigy Industrial Chemicals —
General Aniline & Film Corp. —
Givaudan-Delawanna, Inc. 16
Glycerine Producers' Association —
Goldschmidt Chemical Corp. —

Halby Products Co. —
Heine & Company —
Henkel International GMBH —
Heyden-Newport Chemical Co. —
Hoffman-La Roche, Inc. —
Huisking & Co., Inc., Chas. L. —

International Flavors & Fragrances, Inc. 21

Katz & Co., Dr. Alexander, Div. of F. Ritter & Co. 12
Kenbury Glass Works 81
Kessler Chemical Co., Inc. —
Knapp Products, Inc. —
Kohnstamm & Company 19
Kolar Laboratories, Incorporated —

Lanaetex Products, Inc., The —
Lanitis Bros., Ltd. —
Lautier Fils, Inc. 8
Leberco Laboratories 81
Lehmann, J. M. —
Leonhard Wax Co., T. —
Leuders & Co., George 6

Martinat, Dr. Jean Jacques 81
Maywood Chemical Works, Div. of The Stephan Chemical Co. Cover III
Metal Fabrication Inc. 12
Miranol Chemical Co., The 17
Monsanto Chemical Company —

Naarden —
Norda Essential Oil Co. Cover II
North Broad Labs 81
Noville Essential Oil Co., Inc. —

Old Empire, Inc. 24
Onyx Oil & Chemical Co. —
Frank Orlandi, Inc. —
Owens-Illinois Glass Co. —

Pace Incorporated —
Pacific Vegetable Oil Corp. —
Parento, Inc., Compagnie —
Parsons-Plymouth, Inc., M. W. —
Pathology Associates 81

Peerless Tube Co. —
Perry Bros., Inc. —
Penick & Co., S. B. —
Pennsylvania Refining Company —
P F W 11
Polarome, Inc. —
Precision Valve Corp. —
Protean Chemical Corp. —
Publicker Industries, Inc. 20
Pylam Products, Inc. —

Reheis Co., Inc. 2
Rhodia, Inc. —
Richford Corp. 70
Risdon Manufacturing Co., The —
R. I. T. A. Chemical Corp. —
Ritter & Co., F. 12
Robeco Chemicals, Inc. —
Robinson Wagner Co., Inc. —
Rona Laboratories, Inc. —
Rose Oil Products Co. —
Roubechez, Inc. —
Roure-Dupont, Inc. 13
Ruger Chemical Company, Inc. —

Schimmel & Co., Inc. 18
Scovill Mfg. Co. —
The Sheffield Tube Corporation —
Shulton Inc., Fine Chemicals Div. —
Snell, Foster D. 81
Stecker Chemicals, Inc. —
Stepan Chemical Co. —
Sun-Lac, Inc. 22
Synfleur Scientific Labs, Inc. 9
Syntomatic Corp. —

Thomasson of Pa., Inc. —
Tombarel Products Corp. 3

George Uhe Co., Inc. —
Ungerer & Co. Cover IV
Universal Outlet Co. —

Vanderbilt Co., R. T. 79
Van Dyk Company, Inc. 10
Verley & Company, Albert —
Verona Aromatics, A Div. of Verona-Pharma Chemical Corp. 26
Voisin Restaurant 80

Webb & Co., Inc., R. D. 79
Whittaker, Clark & Daniels —
John Wiley & Sons, Inc. —
Will & Baumer Candle Co., Inc. 12
Wilson–Martin —
Allen B. Wrisley Co. 79

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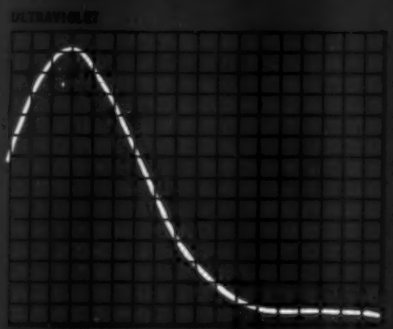
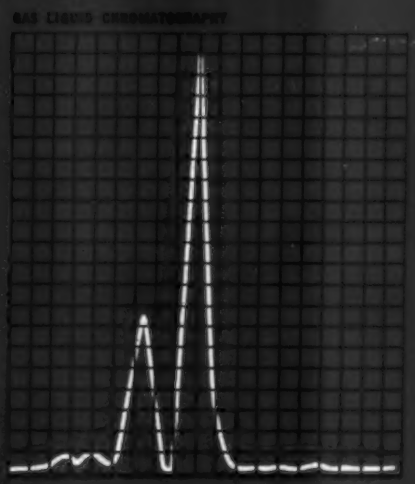
velvety toned, powdery~orris~violet, this alpha isomethyl ionone is the isomer of choice for blending floral, woody, aldehydic or fantasy perfumes... represents the indispensable in the most widely acclaimed creations..... use up to 30%.





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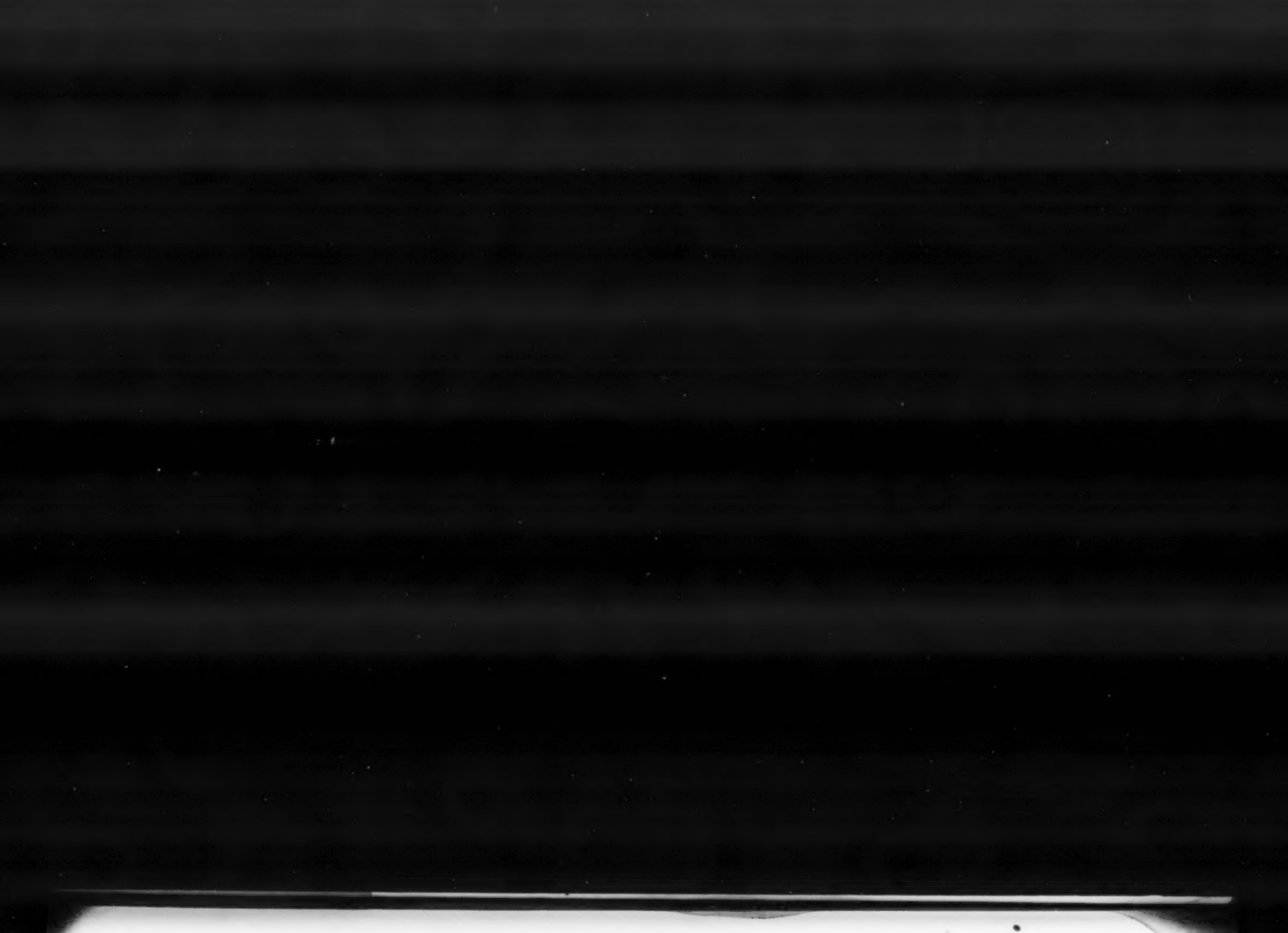
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